AstraZeneca

Advisory Committee Briefing Document	
Drug Substance	Saxagliptin
Date	11 March 2015

SAVOR

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus

sNDAs for Onglyza (22-350/S-014) and Kombiglyze XR (200-678/S-013)

Briefing Document for Endocrinologic and Metabolic Drugs Advisory Committee Meeting

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

EXECUTIVE SUMMARY

Introduction

This briefing document provides background information for the members of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) for a meeting on 14 April 2015, during which the Committee will be asked to discuss the results of AstraZeneca's large (N=16,492) cardiovascular (CV) outcomes trial, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (hereafter referred to as the SAVOR trial), for new drug application (NDA) 22350, ONGLYZA® (saxagliptin) and NDA 200678, KOMBIGLYZE XR® (saxagliptin and metformin HCl extended-release) tablets.

Specifically, this briefing document will focus on the following topics: 1) whether the SAVOR study met the objectives of the 2008 Food and Drug Administration (FDA) Guidance for Industry on treatments for diabetes demonstrating that saxagliptin is not associated with an unacceptable increase in CV risk; 2) results in SAVOR of the secondary endpoint of all-cause mortality and of hospitalization for heart failure (hHF) (a component of a composite secondary endpoint); and 3) results of safety assessments conducted in SAVOR.

This summary of the SAVOR study will show that:

- SAVOR was a well-designed and executed study that was conducted in accordance with the 2008 FDA guidance and met the objective of the guidance by demonstrating that therapy with saxagliptin to treat type 2 diabetes mellitus (T2DM) is not associated with an unacceptable increase in CV risk.

- Saxagliptin therapy did not increase the risk of the composite Major Cardiovascular Event (MACE) endpoint of CV death, non-fatal myocardial infarction (MI), or non-fatal ischemic stroke, meeting the primary safety objective of SAVOR. Additionally, saxagliptin did not increase the risk of an expanded CV composite endpoint, which also included hHF, hospitalization for unstable angina, or hospitalization for coronary revascularization.

- Although a numerical imbalance was observed in all-cause mortality with more events on saxagliptin, CV mortality was balanced. A detailed investigation of the causes of CV and non-CV death indicated that there was no excess mortality attributable to saxagliptin therapy in the SAVOR trial.

- An increased risk for hHF, a component of the balanced secondary endpoint, was observed with saxagliptin treatment. This finding was most relevant for patients at increased risk for heart failure (HF), such as those with a history of HF or renal impairment, and is manageable in the context of the routine care of patients at risk for HF.

- Use of saxagliptin was not associated with an increased risk of lymphopenia, severe infections, opportunistic infections, hypersensitivity reactions, hepatic dysfunction, bone fractures, pancreatitis, renal dysfunction, cancer, or pancreatic cancer.

- Use of saxagliptin was associated with consistent glucose-lowering benefits along with a low risk for hypoglycemia and reductions in microalbuminuria.

Regulatory history

Saxagliptin (Onglyza), a dipeptidyl peptidase-4 (DPP4) inhibitor, was approved in the United States (US) on 31 July 2009 as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. At the time of approval, the efficacy and safety of saxagliptin was established based on the results of 8 Phase 2b/3 clinical studies in over 4600 patients with T2DM. The 2008 FDA guidance was released after the saxagliptin development program for the initial approval of saxagliptin was conducted. In keeping with this guidance, as a condition for saxagliptin approval (a postmarketing requirement [PMR]), AstraZeneca (the Sponsor) was required to perform a CV outcomes study evaluating saxagliptin treatment in high–CV risk patients with T2DM. The SAVOR study was designed by the Thrombolysis in Myocardial Infarction (TIMI) Study Group (an Academic Research Organization of Brigham and Women's Hospital and an affiliate of the Harvard Medical School) and Hadassah Medical Organization in conjunction with the Sponsor to address the PMR. The FDA reviewed the SAVOR protocol and considered it finalized in November 2010. Following the completion of the SAVOR study, AstraZeneca submitted supplemental New Drug Applications (sNDAs) on 28 February 2014 based on results from the study.

SAVOR study design and rationale

SAVOR was a large randomized, double-blind, placebo-controlled Phase 4 study in patients with T2DM at high risk of CV disease (CVD), designed and conducted in accordance with the 2008 FDA guidance, including the use of a blinded Clinical Events Committee (CEC) to adjudicate CV events, the choice of study endpoint, the selection of patient inclusion criteria, and the planned study duration. The primary objective of the study was to evaluate the CV safety of saxagliptin. To do this, the primary endpoint evaluated the effect of saxagliptin on the incidence of the MACE composite endpoint of CV death, non-fatal MI, or non-fatal ischemic stroke. Consistent with the 2008 FDA guidance, the study sought to demonstrate that therapy with saxagliptin would not result in an unacceptable increase in CV risk, based on achievement of an upper bound of the 2-sided 95% CI of risk ratio <1.3 for saxagliptin compared to placebo (non-inferiority). Additionally, the study was designed to test the hypothesis that treatment with saxagliptin would reduce MACE in patients with T2DM compared with placebo (superiority). The statistical plan prespecified a hierarchical testing procedure, with no formal statistical testing with control for multiplicity in the event of a non-statistically significant result for the primary efficacy endpoint; nominal p-values without multiplicity adjustment were to be provided in this case. The study was also required as part of the PMR to evaluate the long-term effects of saxagliptin on safety parameters of interest, including lymphocyte counts, infections, hypersensitivity reactions (including angioedema), liver function, bone fractures, pancreatitis, pancreatic cancer and all malignancies, skin reactions, and renal safety. For details on the SAVOR study design and rationale in the context of the 2008 FDA guidance, see Section 1.4.

SAVOR patient population

SAVOR randomized 16,492 patients ≥40 years of age with documented T2DM (HbA1c >6.5% and <12%) and with either a history of CVD (ischemic heart disease, peripheral vascular disease, and/or ischemic stroke) or multiple risk factors (MRF) for vascular disease (78.6% of patients had CVD at baseline). The study included patients with and without baseline use of oral antidiabetics and/or insulin and medications could be adjusted during the study. A total of 97.6% patients in the saxagliptin group and 97.4% patients in the placebo group completed the study, and a final vital status was obtained for 99.1% of patients. For details for on disposition and demographics of the SAVOR population, see Sections 3.1.1 and 3.1.2.

Results for the primary and secondary composite endpoints of the SAVOR study

The study met the objective of the 2008 FDA guidance by demonstrating saxagliptin was non-inferior to placebo for the primary composite MACE endpoint of CV death, non-fatal MI, or non-fatal ischemic stroke (primary safety objective); hazard ratio (HR) 1.00 (95% CI 0.89, 1.12). Superiority of saxagliptin versus placebo on the composite MACE endpoint was not demonstrated (p=0.986). For the secondary composite endpoint of non-fatal MI, non-fatal stroke, CV death, hHF, hospitalization for unstable angina, or hospitalization for coronary revascularization, no statistically significant treatment differences were observed between saxagliptin and placebo (HR 1.02 [95% CI 0.94, 1.11]; nominal p=0.66 for a difference between the 2 treatment groups). However, for the hHF component of the balanced secondary composite endpoint, more events were observed with saxagliptin treatment (see below). The other secondary endpoint of the SAVOR study was all-cause mortality. The analysis showed a numerical imbalance with more events on saxagliptin (HR 1.11 [95% CI 0.96, 1.27]; nominal p=0.154). For details on the primary and secondary endpoint results, see Section 3.2.

Investigations of all-cause mortality in SAVOR

The Sponsor further explored the numerical imbalance in all-cause mortality observed in SAVOR. Evaluations included assessment of the CV and non-CV categories of death, and detailed exploration of the cases of death within each category. The prespecified component endpoint of CV death was balanced between the saxagliptin and placebo groups (HR 1.03 [95% CI 0.87, 1.22]; nominal p=0.718), consistent with the primary MACE composite endpoint.

A numeric imbalance in non-CV deaths, which was not a prespecified efficacy endpoint, was identified. Adjudicated causes of non-CV death showed numerical imbalances in multiple subcategories between treatments with more fatal events on saxagliptin in the subcategories accident/trauma, hemorrhage, infection, pulmonary failure, and renal failure and more fatal events on placebo in the subcategories gastrointestinal causes, hepatic failure, and malignancy. The types of non-CV death on saxagliptin were varied and without a clear pattern. The subcategory with the largest difference with more events on saxagliptin was deaths due to infection.

A review of the cases of infectious deaths showed that they were unlikely to have a causal relationship to saxagliptin. There was no pattern to the infections; many were associated with other serious events such as a surgical procedure or a hospitalization for another cause. Almost half of the infections that led to death began more than 1 week after last dose of study drug. There was no evidence for an adverse immunologic effect secondary to saxagliptin in patients with a death due to infection based on assessments of lymphocyte counts. And finally, no imbalance in overall severe infections or opportunistic infections was observed in the SAVOR Study.

The results of the evaluation of all-cause mortality indicate that there was no excess mortality attributable to saxagliptin in the SAVOR study. See Section 3.2.2 for the full details of the evaluation of all-cause mortality in SAVOR.

Investigations of hospitalization for HF in SAVOR

In SAVOR, there was an unexpected imbalance in the rate of hHF (HR 1.27 [95% CI 1.07, 1.51]; nominal p=0.007), a component of the balanced secondary composite endpoint, with an excess of 61 cases among patients treated with saxagliptin (n=289/8280) versus placebo (n=228/8212). To further understand the nature of this finding, several questions were addressed to determine 1) whether there is an association between hHF and treatment with saxagliptin and 2) whether patients at high absolute risk for the development of hHF could be identified.

Outside of the SAVOR study, no signal for HF has been observed in preclinical studies or clinical studies or through routine pharmacovigilance. Importantly, no preclinical signals for myocardial injury or adverse effect on myocardial contractility were observed. See Section 5.1.1 for details.

The medical history, initial presentation and hospital course and disposition in patients with a hHF were typical for patients with HF. Regardless of treatment assignment, patients hospitalized for HF had a longer mean duration of diabetes, greater impairment of renal function at baseline, and were more likely to have established CVD at the time of entry into the study compared with patients who were not hospitalized for HF. The clinical presentation and hospital course were also similar between the 2 treatment groups. Patients experiencing a first hHF were at risk for further HF events and/or death as expected for true hHF events. The proportions were similar for both treatment groups. However, because there were more events of hHF among patients who were treated with saxagliptin, numerically more re-hospitalizations for HF and deaths subsequent to the hHF were observed in the saxagliptin group.

Although the relative risk for an initial hHF was similar across patient subgroups, those at high absolute risk of hHF, irrespective of treatment assignment, could be identified by conventional risk factors, especially history of HF and renal impairment. There was a stepwise increase in the risk of hHF in patients who had 0, 1, or 2 of the risk factors of history of HF or significant renal impairment. The majority of patients in SAVOR had neither of these risk factors and were at low absolute risk of hHF. See Section 5.1.3 for details on risk factors for hHF in SAVOR.

Potential etiologies for the hHF finding were explored. No association between hHF and glucose lowering was observed. There was no observed imbalance of adverse events (AEs) suggestive of fluid overload, such as edema, peripheral edema, or increased weight although limitations in study design do not allow definitive conclusions on this potential mechanism. Several lines of evidence indicate the imbalance in hHF observed in SAVOR was not the result of myocyte injury. First, no signal for myocardial injury was observed in preclinical studies. Second, acknowledging that more patients on saxagliptin versus placebo were hospitalized for HF, treatment with saxagliptin did not increase the risk for subsequent hHF or death compared to placebo. This was in the context of a greater rate of study drug discontinuation among placebo-treated patients. And third, biomarker changes of N-terminal prohormone of brain natriuretic peptide (NT-proBNP; a marker of hemodynamic stress), high-sensitivity troponin T (hs-TNT; a marker of myocardial necrosis), and high-sensitivity C-reactive protein (hs-CRP; a marker of inflammation) over time are also consistent with the lack of a direct myocardial effect. See Section 5.1.4 for details on the investigation of potential mechanisms for the imbalance in hHF between treatment arms.

Importantly, in the patients at highest risk for hHF, such as those with a prior history of HF, renal insufficiency, elevated NT-proBNP, or New York Heart Association (NYHA) Class III/IV, the effects of treatment on the primary and secondary composite study endpoints and all-cause mortality endpoint were balanced. See Section 5.1.5 for details of this analysis.

To summarize, in SAVOR, an association between saxagliptin treatment and an increased risk for hHF was observed; however, a mechanism to account for the hHF finding in SAVOR has yet to be determined. Patients with clinical risk factors such as a history of HF or renal impairment are at high absolute risk while patients without these risk factors appeared to be at much lower absolute risk. Thus, given the characteristics of the finding, focused clinical attention to patients at greatest risk for the development of HF is likely to decrease the possibility of hHF occurring in patients on saxagliptin.

Assessment of safety, including PMR-specified events in SAVOR

The results of SAVOR have added substantially to the body of clinical safety information on the use of saxagliptin and provided reassurance regarding the safety and tolerability profile of saxagliptin in patients with T2DM. The incidence of AEs, including serious AEs, AEs leading to discontinuation of study drug, investigator-reported drug-related AEs, and fatal AEs was generally balanced between saxagliptin-treated and placebo-treated patients regardless of age, including the population ≥75 years of age (n=2330 in SAVOR). The results from SAVOR indicate that the occurrence of PMR-prespecified AEs of special interest—which included decreased lymphocytes, severe infections, opportunistic infections, hypersensitivity reactions, liver abnormalities, bone fractures, pancreatitis, skin reactions, renal abnormalities, cancer and pancreatic cancer—was generally balanced between the saxagliptin- and placebo-treated patients. For details on PMR-specified safety evaluations in SAVOR, see Section 6.1.2.

SAVOR results on indices of glucose control and microalbuminuria

In SAVOR, saxagliptin was associated with improved glycemic control despite higher rates of adjustment in other diabetes medications in the placebo group. Specifically, more patients reached HbA1c target <7% without hypoglycemia in the saxagliptin group than in the placebo group (31% versus 24%; nominal p<0.001). Events of hypoglycemia occurred more frequently in patients receiving saxagliptin compared with placebo, but this difference was mostly observed in patients who concomitantly took sulfonylureas and not with other antidiabetic medications. The SAVOR findings support the consistent glycemic benefits with low risk of hypoglycemia observed with saxagliptin across the Phase 2b/3 program conducted in a broad spectrum of patients receiving various background therapies. See Section 7 for details. In addition, use of saxagliptin was associated with reductions in microalbuminuria. Fewer patients in the saxagliptin group compared with placebo progressed from normoalbuminuria to microalbuminuria or from microalbuminuria to macroalbuminuria (see Section 3.3.2).

Summary and conclusions from SAVOR

SAVOR was a well-designed and executed study that was designed in accordance with the 2008 FDA guidance and met the objective of the guidance for demonstrating that therapy with saxagliptin to treat T2DM will not result in an unacceptable increase in CV risk. In addition, use of saxagliptin was not associated with an increased risk of lymphopenia, severe infections, opportunistic infections, hypersensitivity reactions, hepatic dysfunction, bone fractures, pancreatitis, renal dysfunction, cancer, or pancreatic cancer. An association between treatment with saxagliptin and an increased risk for hHF was found in the SAVOR Study. This finding is clinically important and should be communicated appropriately in the Prescribing Information to enable prescribers and patients to minimize the potential for HF hospitalizations with saxagliptin treatment. In conclusion, the SAVOR study has contributed significantly to AstraZeneca's understanding of the safety of saxagliptin. AstraZeneca's clinical program has established the efficacy of saxagliptin in reducing HbA1c and this program along with postmarketing safety data have shown that saxagliptin is well tolerated. The totality of the clinical data with saxagliptin shows that when used according to the label, saxagliptin has a favorable benefit:risk profile and remains an important treatment option for patients with T2DM.

TABLE OF CONTENTS PAGE

EXECUTIVE SUMMARY 2

TABLE OF CONTENTS 8

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 12

1. INTRODUCTION 14

1.1 Purpose of this document 14

1.2 Regulatory background 14

1.3 Saxagliptin for the treatment of T2DM 15
1.3.1 Medical need 15
1.3.2 Clinical profile of saxagliptin 16

1.4 Rationale for the SAVOR study design and conduct 17

2. SAVOR STUDY: DESIGN AND EXECUTION 18

2.1 Methods 18
2.1.1 Study design and oversight 18
2.1.2 Primary objectives and endpoints 20
2.1.3 Statistical analyses 21

3. SAVOR: EFFICACY RESULTS 25

3.1 Study population 25
3.1.1 Patient disposition 25
3.1.2 Demographics and baseline characteristics 28

3.2 Cardiovascular endpoints 30
3.2.1 Primary and secondary composite endpoints 30
3.2.2 Secondary endpoint: time to all-cause mortality 33

3.3 Other efficacy variables 33
3.3.1 Diabetic complications 33
3.3.2 Renal disease progression 33

3.4 Summary and conclusions on efficacy in SAVOR 34

4. SAVOR: ALL-CAUSE MORTALITY DATA 34

4.1 Additional analyses of all-cause mortality 36
4.1.1 Evaluation of CV and non-CV death 38
4.1.1.1 CV death 38
4.1.1.2 Non-CV death 40

4.2 Conclusion on all-cause mortality 43

5. SAVOR: HOSPITALIZATION FOR HEART FAILURE 43
5.1 Investigations of hospitalization for HF in SAVOR 45
5.1.1 Question 1: Is there any other evidence for myocardial injury or HF in association with saxagliptin treatment apart from SAVOR? 46
5.1.2 Question 2: Are the baseline characteristics, clinical presentation, and clinical course for patients with hHF different in patients treated with saxagliptin versus placebo? 47
5.1.3 Question 3: Are there risk factors that would predispose a patient to hHF with saxagliptin versus placebo? 49
5.1.4 Question 4: What other factors have been considered as potential mechanisms for an imbalance in hHF events between the treatment arms? 51
5.1.5 Question 5: Was there any adverse effect on the primary or secondary endpoints (including all-cause mortality) in those patients at greatest risk for hHF? 58
5.1.6 Question 6: How should patients at risk for hospitalization for HF be managed? 63
5.2 Hospitalization for HF: summary and conclusions 63
6. SAVOR: CLINICAL SAFETY RESULTS 64
6.1 Adverse events 64
6.1.1 Overview of adverse events 64
6.1.2 Adverse events of special interest 65
7. SAVOR: GLYCEMIC EFFECTS AND HYPOGLYCEMIA 67
8. CONCLUSIONS FROM SAVOR 69
9. BENEFIT:RISK PROFILE OF SAXAGLIPTIN 70
10. REFERENCES 73

LIST OF TABLES

Table 1 Demographic and baseline characteristics of randomized patients (ITT population) 28
Table 2 Time to first cardiovascular event for the primary and secondary composite endpoints and individual component endpoints (ITT population) 31
Table 3 Time to all-cause mortality by age group (ITT) 38
Table 4 Causes of adjudicated non-CV death in SAVOR 42
Table 5 Selected baseline characteristics for patients hospitalized and not hospitalized for HF in SAVOR (ITT) 48

Table 6 Events subsequent to an adjudicated hHF event: rehospitalization for hHF, mortality, and discontinuation of study drug 55

Table 7 Overall summary of adverse events (ITT population)............................65

LIST OF FIGURES

Figure 1 HbA1c effects in saxagliptin clinical studies 16

Figure 2 Overview of SAVOR study design 20

Figure 3 SAVOR patient disposition (ITT population) 26

Figure 4 Kaplan-Meier estimate of time to discontinuation of study drug in SAVOR..27

Figure 5 Sensitivity analyses of the primary and secondary composite endpoints...32

Figure 6 Kaplan-Meier estimate of cumulative percent of time to all-cause mortality (ITT population)..35

Figure 7 Forest plot of the hazard ratio of sensitivity analyses for all-cause mortality 36

Figure 8 Kaplan-Meier estimate of cumulative percent of time to CV death (ITT population) 39

Figure 9 Forest plot of the hazard ratio for CV death split by reasons of death 40

Figure 10 Kaplan-Meier estimates of cumulative percent of time to non-CV death (ITT population)...41

Figure 11 Kaplan-Meier estimate for adjudicated hospitalization for HF over time in the ITT period in SAVOR...44

Figure 12 Risk of hospitalization for heart failure in patients with and without baseline risk factors (eGFR ≤60 mL/min or history of HF)........50

Figure 13 Risk of hospitalization for HF by baseline NT-proBNP quartile (ITT population) 51

Figure 14 Change in median NT-proBNP from baseline to year 2/ EoT overall and in patients with or without history of HF 56

Figure 15 Median hs-TNT and hs-CRP at baseline and at year 2/EoT (ITT population)...57

Figure 16 Primary composite endpoint in patients at high risk for HF....................59

Figure 17 Secondary composite endpoint in patients at high risk for HF................60

Figure 18	All-cause mortality in patients at high risk for HF	61
Figure 19	Outcomes in patients with NYHA III/IV HF at baseline	62
Figure 20	Forest plot of hazard ratio for adverse events of special interest (ITT population)	66
Figure 21	Hypoglycemia events (ITT population)	68
Figure 22	Hazard ratio of time to first event of any hypoglycemia by baseline antidiabetes medication (ITT)	69

LIST OF APPENDICES

Appendix A Properties of available glucose-lowering agents

Appendix B SAVOR TIMI 53 Publications

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and special terms are used in this Briefing Document:

Abbreviation or special term	Explanation
ACE	Angiotensin-converting enzyme
AE	Adverse event
AEOSI	Adverse event(s) of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
CEC	Clinical Event Adjudication Committee
CI	Confidence interval
CRF	Case report form
CV	Cardiovascular
CVD	Cardiovascular disease
DPP4	Dipeptidyl peptidase-4
eGFR	Estimated glomerular filtration rate
EMDAC	Endocrinologic and Metabolic Drugs Advisory Committee
EoT	End of treatment
FDA	Food and Drug Administration (United States)
GLP-1	Glucagon-like peptide-1
HbA1c	Glycosylated hemoglobin
HF	Heart failure. The term "heart failure (HF)" is used in place of "congestive heart failure (CHF)" which may have been used in the SAVOR study case report forms and in SAVOR study databases.
hHF	Hospitalization for heart failure Unless otherwise specified, "hospitalization for HF" refers to the first hospitalization for HF.
HOMA2-β	Homeostasis model 2 assessment beta-cell function
HR	Hazard ratio
hs-CRP	High-sensitivity C-reactive protein

Abbreviation or special term	Explanation
hs-TNT	High-sensitivity cardiac troponin T
ITT	Intention-to-treat
MACE	Major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mITT	Modified intention-to-treat (defined as On-treatment + 30 days)
MRF	Multiple risk factors
NLR	Neutrophil/lymphocyte distribution ratio
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
PMR	Postmarketing requirement
PP	Per protocol
PT	Preferred term
RDW	Red cell distribution width
SAE	Serious adverse event
SAVOR	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus
SMQ	Standardized MedDRA Query
sNDA	Supplemental New Drug Application
SOC	System organ class
SU	Sulfonylurea
T2DM	Type 2 diabetes mellitus
TIMI	Thrombolysis in Myocardial Infarction (study group)
TZD	Thiazolidinedione
US	United States

1. INTRODUCTION

1.1 Purpose of this document

This briefing document provides background information for the members of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) for a meeting on 14 April 2015, during which the committee will be asked to discuss the results of AstraZeneca's Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus clinical trial (SAVOR), for new drug application (NDA) 22350, ONGLYZA® (saxagliptin) and NDA 200678, KOMBIGLYZE XR® (saxagliptin and metformin HCl extended-release) tablets. SAVOR is a large cardiovascular (CV) outcomes study designed in accordance with the 2008 Food and Drug Administration (FDA) guidance to demonstrate that a new antidiabetic therapy to treat type 2 diabetes mellitus (T2DM) is not associated with an unacceptable increase in CV risk. SAVOR was conducted as part of a Postmarketing Requirement (PMR).

Specifically, this briefing document will focus on the following topics:

- Whether the SAVOR study met the objectives of the 2008 Food and Drug Administration (FDA) Guidance for Industry (FDA Final Guidance on Diabetes Mellitus 2008) demonstrating that saxagliptin is not associated with an unacceptable increase in CV risk

- Results in SAVOR of the secondary endpoint of all-cause mortality and on hospitalization for heart failure (hHF) (a component of a composite secondary endpoint)

- Results of safety assessments conducted in SAVOR as part of the PMR

1.2 Regulatory background

Saxagliptin, a dipeptidyl peptidase-4 (DPP4) inhibitor, was approved as Onglyza in the United States (US) on 31 July 2009 as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Subsequently on 05 November 2010, the fixed-dose combination product of saxagliptin plus metformin extended release (Kombiglyze XR) was approved in the US. Onglyza is now approved in over 90 countries worldwide. The recommended dose for Onglyza is 2.5 or 5 mg once daily with 2.5 mg once daily recommended for patients with moderate, severe, or end stage renal disease.

The saxagliptin clinical development program supporting initial approval was conducted prior to release of the 2008 FDA Guidance for Industry (FDA Final Guidance on Diabetes Mellitus 2008). A post-hoc analysis of CV events based on the submission data met the criteria for product approval (Frederich et al 2010). Additionally, the EMDAC Advisory Committee of 01 April 2009 recommended a postmarketing CV outcomes study. In keeping with the 2008 FDA guidance, as a condition for saxagliptin approval (PMR), AstraZeneca (the Sponsor) was required to perform a Phase 4, randomized, double-blind controlled study evaluating the effect of saxagliptin on the incidence of major adverse cardiovascular events (MACE) in patients with T2DM. The study was required, as part of the PMR, to include assessments of the long-term effects of saxagliptin on safety parameters of interest, including lymphocyte counts, infections, hypersensitivity reactions (including angioedema), liver function, bone fractures, pancreatitis, pancreatic cancer and all malignancies, skin reactions, and renal safety. Because renal impairment is an important complication of diabetes, the Sponsor was requested to ensure that there would be a minimum of 1 year of exposure for at least 200 saxagliptin-treated patients with moderate renal impairment and at least 100 saxagliptin-treated patients with severe renal impairment. The Sponsor was asked to recruit approximately 30% of the total cohort of patients in North America and that patients enrolled in the study should be representative of the types of patients from the US who are likely to be prescribed Onglyza.

The SAVOR study was designed by the Thrombolysis in Myocardial Infarction (TIMI) Study Group (an Academic Research Organization of Brigham and Women's Hospital and an affiliate of the Harvard Medical School) and Hadassah Medical Organization in conjunction with the Sponsor to address the PMR. The Sponsor tracked the progress of all aspects of the study through academic steering committees, maintained contact with the FDA, provided monitoring support and study drug, and reviewed all papers, abstracts, and presentations.

The SAVOR protocol to address the PMR for a CV outcomes study was reviewed and considered final by the FDA on 23 November 2010. The Sponsor submitted supplemental New Drug Applications (sNDAs) for Onglyza and Kombiglyze on 28 February 2014 based on results from the completed SAVOR study.

1.3 Saxagliptin for the treatment of T2DM

1.3.1 Medical need

T2DM is a chronic progressive disease, characterized by hyperglycemia and an increased risk of microvascular and macrovascular complications. Achieving and maintaining glycemic treatment goals is challenging (ADA 2015). The treatment limitations of older classes of antidiabetes medicines, related to adverse effects such as weight gain and increased risk of hypoglycemia, can contribute to the poor level of glycemic control seen worldwide (ADA 2015; see Appendix A, Table 1 for a summary of the advantages and disadvantages of available glucose-lowering agents).

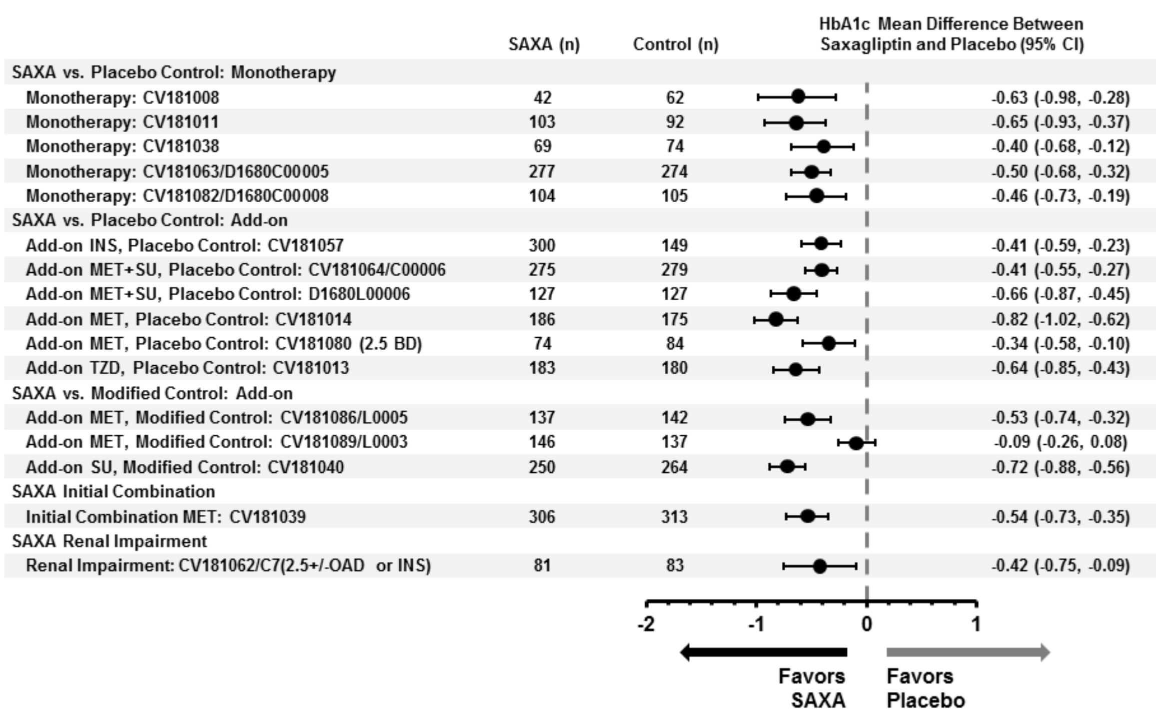
Numerous randomized, controlled clinical studies have demonstrated conclusively that intensive and long-term improvement in glucose control, assessed as glycosylated hemoglobin (HbA1c), reduces microvascular complications in both type 1 and type 2 diabetes (Skyler et al 2009, FDA Draft Guidance on Diabetes Mellitus 2008, ADA 2015). For example, in the Diabetes Control and Complications Trial (DCCT), patients with type 1 diabetes who achieved intensive glycemic control showed an approximate 60% reduction in development or progression of diabetic retinopathy, nephropathy, and neuropathy compared with a group with standard glycemic control (DCCT 1993, Skyler et al 2009). Similarly, in the UK Prospective Diabetes Study (UKPDS) conducted in patients with T2DM, long-term enhanced glycemic control (HbA1c ≤7%) was associated with a 25% reduction in microvascular complications compared with standard treatment (UKPDS Group 1998). Therefore, treatments that can achieve lower HbA1c levels while presenting a low risk for hypoglycemia and other adverse effects are needed.

1.3.2 Clinical profile of saxagliptin

Saxagliptin is an important tool in the treatment of diabetes, providing consistent glucose-lowering across a broad spectrum of patients with diabetes, with lower risk for adverse effects (including hypoglycemia and weight gain) than with some other antihyperglycemic agents.

At the time of FDA approval of Onglyza, results from 8 Phase 2b/3 clinical studies in the saxagliptin clinical development program, conducted in over 4600 patients, supported the efficacy of saxagliptin in a wide range of patients with T2DM, as monotherapy, as add-on therapy to metformin, a sulfonylurea (SU), a thiazolidinedione (TZD), or insulin, and as initial therapy in combination with metformin. Since then, additional studies were conducted to provide further efficacy and safety data. In clinical studies, patients taking saxagliptin have demonstrated a mean decrease of HbA1c of 0.4% to 0.8% compared with placebo, HbA1c reductions typical for a DPP4 inhibitor. Figure 1 summarizes the reductions in HbA1c observed in the 16 Phase 2b/3 placebo-controlled studies of saxagliptin given as monotherapy; as add-on combination treatment to metformin, TZD, or an SU; as initial combination therapy with metformin; or in patients with renal impairment.

Figure 1 HbA1c effects in saxagliptin clinical studies



In modified control studies, saxagliptin as add-on therapy to moderate doses of metformin or SU was compared with upward-titrated metformin or SU.

CI Confidence interval; HBA1c Glycosylated hemoglobin; Ins Insulin; Met Metformin; OAD Oral antidiabetic; SAXA Saxagliptin; SU Sulfonylurea.

Saxagliptin also has a well-established safety profile, with a low risk of hypoglycemia and weight neutrality (Hirshberg et al 2014). The safety and tolerability profile of saxagliptin continues to be supported by extensive on-market experience. Since the 2009 approval of saxagliptin as Onglyza in the US and subsequent approval in over 90 countries worldwide, as well as approval of Kombiglyze XR in 2010, over 4 million patients have taken saxagliptin.

1.4 Rationale for the SAVOR study design and conduct

SAVOR was designed and conducted in accordance with the 2008 FDA guidance to demonstrate that saxagliptin treatment is not associated with an unacceptable increase in CV risk (FDA Final Guidance on Diabetes Mellitus 2008) and to address the Onglyza PMR for a CV outcomes study. The following 2008 FDA guidance recommendations were implemented in SAVOR:

- Use of a blinded, independent Clinical Events Committee (CEC) to prospectively adjudicate CV events during the study. These included all deaths, myocardial infarction (MI), stroke, hospitalization for unstable angina, hHF and hospitalization for revascularization procedures, and pancreatitis.

- Protocol design and planned statistical methodology agreed in advance with the FDA. The study was adequately powered to definitively show that the upper bound of the 2-sided 95% confidence interval (CI) for the estimated risk ratio is <1.3 for the MACE endpoint.

- Inclusion of a large proportion of patients at high risk for CV events, including patients with advanced T2DM, patients with moderate and severe renal failure, patients with established CVD including heart failure (HF), and patients ≥65 years of age

- A study with sufficient duration to obtain both exposure and enough events to provide data on longer-term CV risk

In addition to the recommendations in the 2008 FDA guidance, the FDA provided important advice to the Sponsor regarding study design and statistical analysis planning, which was also incorporated into the final SAVOR study protocol and statistical methodology. This included specific FDA recommendations aimed at enhancing the robustness of the study to ensure enrollment of sufficient numbers of patients at sites in North America (30%) and from minority groups, and to provide a more thorough assessment of specific adverse events (AEs) of interest relevant to the use of saxagliptin or antidiabetic agents in general. The adverse events of special interest (AEOSI) included lymphopenia, severe infections, opportunistic infections, hypersensitivity reactions, hepatic dysfunction, bone fractures, pancreatitis, renal dysfunction, cancer, and pancreatic cancer. To assess the impact of saxagliptin on CV safety, SAVOR utilized the composite endpoint of CV death, non-fatal MI, or non-fatal ischemic stroke because it is the most rigorous way to assess CV effects of any given treatment (EMA Revised Guidance on Diabetes Mellitus 2012, FDA Final Guidance on Diabetes Mellitus 2008).

While a non-inferiority trial design would suffice to meet the requirements of the 2008 FDA Guidance, a meta-analysis of data from the Phase 3 program suggested that saxagliptin might have CV benefit. Thus, the SAVOR study was designed to evaluate both non-inferiority and superiority of saxagliptin to placebo on the primary endpoint. At the time of approval, the saxagliptin development program had not identified any preclinical or clinical CV safety signals. In a published 8-study meta-analysis of CV data (Frederich et al 2010, Cobble and Frederich 2012), patients treated with saxagliptin had a lower rate of MACE compared with control with an incidence rate ratio (IRR) of 0.45 (95% CI 0.24, 0.83). In a subsequent meta-analysis based on a 20-study pool of saxagliptin studies, MACE IRR was 0.74 (95% CI 0.45, 1.25) (Iqbal et al 2014), although it should be kept in mind that both analyses were retrospective in nature, involving relatively short follow-up times (follow-up time for saxagliptin and control was 6051 and 2869 patient-years, respectively, in the 20-study pool). The decision to include a superiority assessment of CV safety in SAVOR is important because despite data with other antidiabetic drugs showing the benefits of HbA1c reduction on microvascular disease (Skyler et al 2009, FDA Draft Guidance on Diabetes Mellitus 2008), no studies have documented the benefits on CV macrovascular disease with an antidiabetic therapy.

Since the glycemic efficacy and overall safety of saxagliptin were previously established in the saxagliptin program, certain design elements were incorporated to help maintain patients in the study and simulate a real-world setting. In SAVOR, patients were permitted background glucose-lowering therapies that could be adjusted as needed during the study, with the exception of other DPP4 inhibitors or glucagon-like peptide-1 (GLP-1) mimetics. This design feature would tend to reduce differences in HbA1c between the treatment arms and therefore the likelihood of observing a microvascular or macrovascular benefit secondary to glucose lowering. However, if a macrovascular benefit was observed, the likelihood that it was secondary to saxagliptin treatment would increase. Another important element of the SAVOR design to maintain patients in the study was to minimize clinical visits and thus the burden of participating in a long-term randomized clinical trial. Clinic visits were scheduled at 6-month intervals with telephone contacts every 3 months between visits.

2. SAVOR STUDY: DESIGN AND EXECUTION

2.1 Methods

2.1.1 Study design and oversight

SAVOR was a multicenter, randomized, double-blind, placebo-controlled Phase 4 study designed to exclude unacceptable CV risk with saxagliptin treatment and to evaluate whether treatment with saxagliptin, when added to current background therapy, can reduce the composite endpoint of CV death, non-fatal MI, or non-fatal ischemic stroke in patients with T2DM at high risk of CV disease (CVD).

Eligible patients were ≥40 years of age, had documented T2DM (HbA1c >6.5% and <12%), and also had either a history of established atherosclerotic CVD (ischemic heart disease, peripheral vascular disease, and/or ischemic stroke) or multiple risk factors (MRF) for vascular disease (men ≥55 years of age or women ≥60 years of age and at least one of the following: dyslipidemia, hypertension, currently smoking). Patients continued their background diabetes medication, which could be adjusted by discontinuing or changing the dose or by adding other diabetes medications (except for other DPP4 inhibitors or GLP-1 mimetics) to achieve or maintain glycemic control. All patients were to be treated in accordance with regional standards of care for CV risk factors (eg, hypertension, dyslipidemia) and HbA1c, and dietary and lifestyle modifications were reinforced.

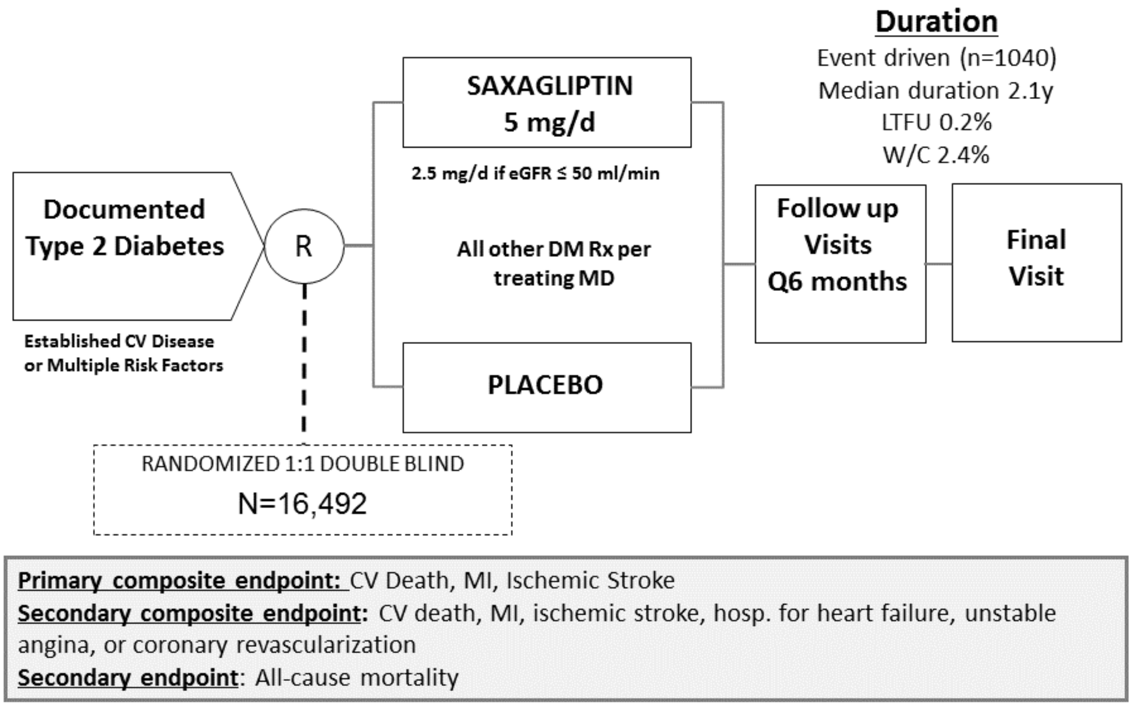
Patients were randomized in a 1:1 ratio to receive either saxagliptin (5 mg in patients with normal renal function and mild renal impairment and 2.5 mg in patients with moderate or severe renal impairment) or placebo once daily. Randomization was stratified by CV risk category, ie, a history of established atherosclerotic CVD or MRF for vascular disease. Randomization was further stratified by baseline renal impairment category (normal renal function and mild renal impairment [estimated glomerular filtration rate (eGFR) >50 mL/min], moderate renal impairment [eGFR 30 to 50 mL/min], or severe renal impairment [eGFR <30 mL/min], excluding patients on chronic dialysis).

SAVOR was an event-driven study powered to test for both non-inferiority and superiority of saxagliptin to placebo treatment. The planned sample size of 16,500 randomized patients was intended to yield approximately 1040 primary composite endpoint events and to provide at least 98% power to test the non-inferiority of saxagliptin versus placebo (primary safety objective) at the 2.45% 1-sided level and 85% power to test for superiority of saxagliptin versus placebo at the 2.45% 1-sided level assuming a 17% reduction in risk in the saxagliptin group (primary efficacy objective). An interim analysis for superiority was performed when 50% of the total number of primary endpoint events was accrued (ie, at 520 events).

The total number of planned randomized patients, 16,500, was to include no more than approximately 15,700 patients with normal renal function or mild renal impairment (eGFR >50 mL/min), to ensure that at least 800 patients with moderate to severe renal impairment (eGFR ≤50 mL/min) were included. The study design ensured the inclusion of 300 patients with severely impaired renal function. Once 300 patients with severe renal impairment (eGFR <30 mL/min) were randomized, no additional patients with severe renal impairment were to be enrolled. A minimum of 30% of the randomized patients were to come from North America (US and Canada) sites, as well as adequate numbers of African-American patients in the US, patients of Hispanic ethnicity, and men and women ≥65 and ≥75 years of age.

Figure 2 provides an overview of the SAVOR study design.

Figure 2 **Overview of SAVOR study design**



CV Cardiovascular; d Day; DM Diabetes mellitus; hosp Hospitalization; LTFU Lost to follow-up; MD Physician; MI Myocardial infarction; n, N Number of patients; Q6 months Every 6 months; R Randomization; Rx Prescription; W/C Withdrew consent; y Years.

An independent Data Monitoring Committee, a blinded and independent CEC, and Executive and Steering Committees were selected by the study Sponsor and the academic leadership (TIMI Study Group and Hadassah Medical Organisation) to provide study oversight and/or assess the safety and efficacy data and decide when stopping rules were met. The task of the CEC was to adjudicate the events of the primary and secondary endpoints and pancreatitis in a consistent and unbiased manner throughout the study; all patient data sent to the CEC were blinded with respect to both patient identification and treatment assignment.

2.1.2 Primary objectives and endpoints

In the SAVOR study, the time to first occurrence of an event from the composite endpoint of CV death, non-fatal MI, or non-fatal ischemic stroke was both the primary safety variable and the primary efficacy variable. The primary analysis first evaluated the safety of saxagliptin with a non-inferiority analysis and then tested the superiority of saxagliptin versus placebo to address the primary objectives:

- The primary safety objective was to establish the upper bound of the 2-sided 95.1% CI for the estimated risk ratio comparing the incidence of the composite endpoint of

CV death, non-fatal MI, or non-fatal ischemic stroke observed with saxagliptin to that observed in the placebo group was less than 1.3.

- The primary efficacy objective was to determine, as a superiority assessment, whether treatment with saxagliptin compared with placebo when added to current background therapy would result in a reduction in the composite endpoint of CV death, non-fatal MI, or non-fatal ischemic stroke in patients with T2DM.

Secondary endpoints are described in conjunction with the analysis results summarized in Section 3 (efficacy) and Section 6 (safety).

See Appendix B, Scirica et al 2011 (Appendix C in that publication) for a full list of efficacy and safety endpoints in SAVOR.

Definitions of the CV endpoints assessed in SAVOR were developed to be consistent with the definitions in the Standardized Definitions for End Point Events in Cardiovascular Trials draft guidance from the FDA (Hicks et al 2010). See Appendix B, Scirica et al 2011 (Appendix B in that publication) for full definitions of CV events assessed in SAVOR.

See Appendix B, Scirica et al 2013 for a report of the primary findings from SAVOR and Scirica et al 2014 for a report of findings on hHF, as analyzed independently by TIMI. The first publication documents important protocol amendments made prior to database lock, including elevation of the all-cause mortality endpoint to a secondary efficacy objective (originally categorized as “Other”). Note that there are some slight differences between the data in TIMI’s analyses in both publications when compared with those of the Sponsor, but conclusions from both sets of analyses are consistent.

2.1.3 Statistical analyses

Analysis populations

The following analysis populations were defined for the SAVOR study:

- The **intention-to-treat (ITT)** population (primary analysis) was defined as all randomized patients and was the primary analysis set for the primary and secondary analyses. Patients were analyzed according to the treatment group to which they were randomized.

- The **per protocol (PP)** population was defined as all randomized patients excluding patients with important protocol deviations.

- The **modified ITT (mITT [on treatment])** population was defined as all randomized patients who received at least 1 dose of study drug. Analyses used an on-treatment method to include only those events that occurred on or after the first dose and/or on or before 30 days after the last dose of study drug (similar to the definition for on-treatment SAEs). Patients were analyzed according to the treatment group to which they were randomized.

The SAVOR trial included a variety of research hypotheses. For each hypothesis, a number of analysis populations could be considered. A unifying approach to the analysis populations was developed in the statistical analysis plan to simplify the overall framework, recognizing that in isolation, individual hypotheses might be best served from one of the alternative populations.

In this framework, the ITT population was used for the primary analyses of all hypothesis tests, as it provides an overall evaluation of the effect of saxagliptin or placebo as a treatment regimen in a real-world setting, as well as reduces the potential bias caused by censoring events and patients as a result of differences in study drug adherence. The mITT and PP analyses were also provided as part of the robustness evaluation, especially relevant for the non-inferiority hypothesis. For this objective, the choice of ITT was driven by the nested superiority test to follow the initial non-inferiority hypothesis test. In absence of the nested test, the on-treatment population is usually recognized as the key population for interpretation and is important to the interpretation of the data for this hypothesis.

Please note, the SAVOR governance committees suggested the nomenclature of 'mITT' for what is an 'on treatment plus 30 days' population, recognizing this was a hybrid approach, as 30 days extended beyond the usual 5 half-lives on an on-treatment definition. This nomenclature has been in place since the protocol was finalized and has been consistently used since then.

Primary and secondary analyses

The ITT was used for the primary analysis and compared the time from randomization to the first occurrence of an event in the primary composite endpoint (CV death, non-fatal MI, or non-fatal ischemic stroke) between treatments using the Cox proportional hazards model stratified by baseline CV risk group and baseline renal function category, with treatment as a model term.

The primary analysis was performed in a sequential stepwise fashion to control for Type I error by first evaluating the safety of saxagliptin with a non-inferiority analysis. The non-inferiority analysis sought to establish the CV safety of saxagliptin by demonstrating that the upper bound of the 2-sided 95.1% CI for the estimated risk ratio comparing the incidence of the composite endpoint of CV death, non-fatal MI, or non-fatal ischemic stroke observed with saxagliptin to that observed in the placebo group was <1.3. The test had higher power than the superiority test and is the required test per the 2008 FDA guidance. The guidance required that the upper bound of the CI for the hazard ratio (HR) be <1.3. Superiority for the primary endpoint was tested next, followed by superiority for the secondary composite MACE endpoint and finally, superiority for all-cause mortality. The primary non-inferiority and superiority hypotheses were tested at the significance level of 2.45% (1-sided) in order to account for the interim analysis for superiority that was performed when 50% of the total number of primary endpoint events was accrued (ie, at 520 events). For the final analysis, HRs and 2-sided 95.1% CIs were reported.

The secondary efficacy variables were analyzed similarly to the primary efficacy variable.

Sensitivity analyses

The mITT and PP sensitivity analyses were conducted in addition to the ITT analysis to provide an additional evaluation of "pharmacologic effect" (Lachin 2000). However, all 3 analyses have features that are relevant to the interpretation. Results from the mITT and the PP analyses need to be interpreted carefully, taking into consideration the specific study design and its potential impact on study results. Similar to other outcome studies, SAVOR was designed to allow background medication changes while patients received blinded medication. With this design, the mITT analysis is subject to a potential bias due to imbalance/difference in the change of background medication between treatment groups, especially when one of the arms is a long-term placebo in a disease setting that requires adjustments to background medications. Indeed, the study was designed to allow change of background medication in order to minimize discontinuation of study medication, overall and between treatments. Discontinuation, especially if occurring unequally between treatment groups (as was the case in SAVOR, see Section 3.1.1), would cause attrition bias for any on-treatment analysis. Therefore, results of the mITT or PP analyses need to be interpreted with caution. For the primary and secondary endpoint analyses, the ITT analysis provided an overall evaluation for saxagliptin versus placebo as a treatment regimen in a real-world setting, although it could be argued, the extension of the observation period could drown out a true acute drug effect for which other short-term clinical trials would be helpful for context. It was, however, the primary analysis designated by design, as its inclusiveness outweighed the potential downside.

Subgroup analyses of the primary and secondary endpoints

Prespecified subgroups examined included baseline CV risk category and baseline renal function category (and baseline CV risk category by renal function category); age, gender, race, region, baseline number of risk factors, baseline duration of T2DM, history of HF, baseline diabetes medications, and baseline CVD medications including combinations. The CIs for these subgroup analyses were not adjusted for multiple comparisons and were interpreted only descriptively; p-values were provided for treatment-by-subgroup interactions only.

Safety analyses

Adverse events were summarized as on treatment and overall. The on treatment category of AEs included AEs with onset on or after the first study drug dosing date and on or before the first day (30th day for serious AEs [SAEs]) after the last blinded study drug dosing date or the study completion date, whichever was earlier, and excluded AEs that occurred after the patient had discontinued randomized study drug. The overall AE category included all AEs on or after randomization, regardless of whether or not the patient had received and/or discontinued randomized study drug.

Post-hoc exploratory analyses

In some areas (see Section 4and Section 5), post-hoc exploratory analyses were conducted in an attempt to further characterize the observations in the study. Strengths of these analyses include the ability to utilize the substantial amount of data available from this large CV outcomes study. The limitations are that these analyses are often data-driven, with no adjustment possible for multiplicity. Due to the large number of subgroups tested and multiple endpoints evaluated in these analyses, there is a high likelihood that some findings are due to chance.

Except as otherwise noted, the principles for such analysis methods were consistent with those for the overall study. Models generally included the randomization stratification variables, except in cases when one or both of the stratification variables were included (in either continuous or categorical form) as a predictor. In those cases where a set of models were analyzed and any of the models used stratification variables as predictors, all models were fit without stratification to maintain comparability between models.

For hHF, a piecewise proportional hazard model was used to further characterize the treatment difference over time given that the test of proportionality was significant (p=0.03). Note that in a piecewise proportional hazard model, the estimate hazard in second segment (after 270 days) is not informed by the data in the first segment (before 270 days) and results such an analysis should be considered descriptive and interpreted carefully (see Section 5.1 for this analysis).

Post-hoc biomarker evaluation

The biomarkers N-terminal prohormone of brain natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T (hs-TNT), and high-sensitivity C-reactive protein (hs-CRP) are useful in the diagnosis and assessment of prognosis in patients with HF (Braunwald 2013) and were evaluated in SAVOR. For each biomarker, baseline was defined as the value obtained prior to dosing of study treatment. Descriptive statistics, based on biomarker data available from consenting patients, were calculated for all 3 biomarkers at baseline and Year 2/End of Treatment (EoT), with values collected for more than 14 days after the last dose of study drug excluded. An analysis of covariance (ANCOVA) was performed to test for treatment differences in the change from baseline to Year 2/EoT for each biomarker. The ANCOVA model included terms for the baseline value of the biomarker and treatment. Cox proportional hazards models were fit for the primary and secondary endpoints, time to CV death and hHF, with a covariate for the 1st through 4th quartile of each biomarker's baseline value. Interactions between the baseline biomarker and treatment were tested.

Post-hoc reassessment of adjudicated events by TIMI

Positively adjudicated events were reviewed by TIMI using existing packets of information for these events. The purpose of the reassessment was to gain a better understanding of the clinical characteristics of the patients who were adjudicated as being hospitalized for HF. The listing of identified events was provided to TIMI CEC and the adjudication remained consistent with the adjudication process outlined in the CEC Charter.

3. SAVOR: EFFICACY RESULTS

3.1 Study population

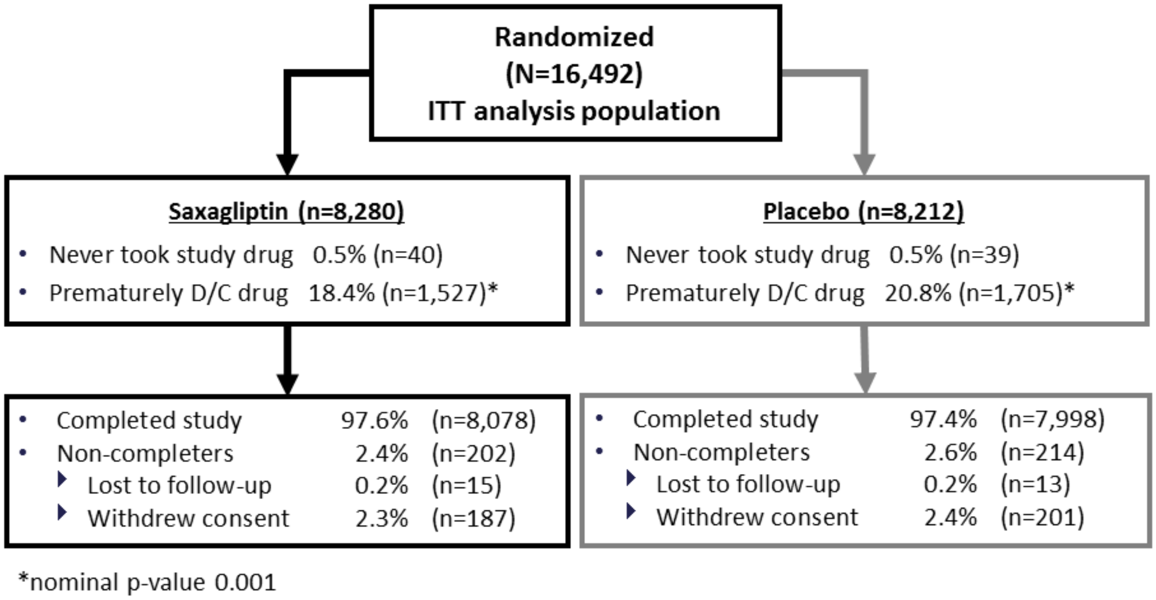
The SAVOR study randomized a total of 16,492 patients from 788 sites in 26 countries, which included 321 sites in North America (271 sites in the US and 50 sites in Canada). Randomization targets with respect to region, CV risk categories, and renal function were met and evenly distributed between the 2 treatment groups. Of all randomized patients, 31.9% and 42.2% were enrolled at sites in North America and Europe, respectively, with the remaining patients enrolled at sites in Latin America and Asia/Pacific regions. With respect to baseline CV risk categories, 78.6% of randomized patients had established CVD, and 21.4% had MRF. A total of 12.8% of patients had a history of HF. Overall, 13.6% and 2% of randomized patients had moderate and severe renal impairment at baseline, respectively. Overall, 51.9% of the patients were ≥65 years of age and 14.1% were ≥75 years of age.

The randomized patient population met the recommendations of the 2008 FDA guidance for inclusion of a large proportion of patients at high risk for CV events, including those with advanced T2DM, moderate or severe renal impairment, and established CVD, as well as patients ≥65 years of age.

3.1.1 Patient disposition

Of the randomized patients, 99.5% in each treatment group received at least 1 dose of study drug and 97.5% completed the study (see Figure 3). A final vital status was obtained for 99.1% of patients. All vital status data for withdrawn patients is from publicly available sources. Overall, this was a robust, well executed study with minimal patients lost to follow-up.

Figure 3 SAVOR patient disposition (ITT population)

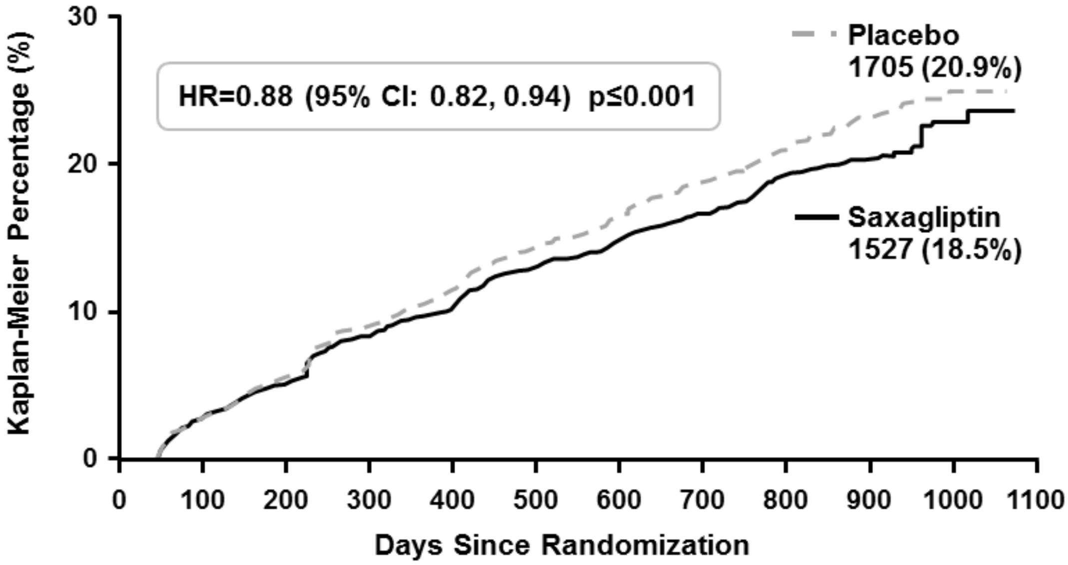


Note: Category of withdrew consent includes subject withdrew consent and administrative withdrawal.
D/C Discontinued; ITT Intention-to-treat.

Patient disposition for the ITT population was similar for the 2 treatment groups, overall and in each of the baseline CV risk and renal function categories.

The proportion of patients who prematurely discontinued from treatment was 18.4% (n=1527) in the saxagliptin group and 20.8% (n=1705) in the placebo; a post-hoc statistical comparison yielded a nominal p-value of 0.001 (Figure 4).

Figure 4 **Kaplan-Meier estimate of time to discontinuation of study drug in SAVOR**



Number of Patients at Risk*

Saxagliptin	8240	7872	7568	7353	7094	6741	6323	4859	2948	701	13	0
Placebo	8173	7808	7482	7255	6975	6605	6183	4722	2820	692	9	0

***Number of patients at risk are ITT patients taking at least one does of study drug.**

CI Confidence interval; HR Hazard ratio; Intention-to-treat.

The proportion of patients who permanently discontinued study drug and their reasons for discontinuation were similar for the 2 treatment groups. Note that Figure 4 is based on the ITT population and includes patients who took at least 1 dose of blinded medication (40 and 39 patients never took study medication in saxagliptin and placebo treatment, respectively). The most frequently reported reason for discontinuation of study drug was patient decision (11.1% [n=920] and 13.2% [n=1087] in the saxagliptin and placebo groups, respectively). Most patients who discontinued from the study withdrew consent (2.3% [n=187] and 2.4% [n=201] in the saxagliptin and placebo groups, respectively).

The overall mean duration in the study (time from randomization to last study contact) for the ITT population was 2.0 years in each treatment group. The duration was similar for patients in each treatment group across renal function categories.

Mean exposure to study drug (regardless of interruptions) was 1.82 and 1.81 years/patient for the saxagliptin and placebo groups, respectively, and 1.82 years/patient for the full ITT population. Approximately 78% of patients took study drug for at least 1.5 years, and over 40% of the population was exposed to study drug for 2 to 3 years, resulting in 15,030.2 versus 14,775.1 patient-years of exposure for the saxagliptin and placebo groups, respectively. Mean exposure to study drug was similar between the saxagliptin and placebo groups across all 3 categories of baseline renal function (normal function to mild impairment, moderate impairment, severe impairment). Most patients in each category took study drug for at least 1.5 years. In the moderate and severe categories of renal impairment, 934 and 137 patients, respectively, were exposed to saxagliptin for at least 1 year, and 433 and 77 patients, respectively, were exposed for 2 to 3 years.

3.1.2 Demographics and baseline characteristics

The 2 treatment groups were generally well balanced for demographic, baseline, and diabetes characteristics, which were representative of adult patients with T2DM and at high risk for CVD (see Table 1 for a summary of selected patient characteristics by treatment group for the ITT population).

Table 1 Demographic and baseline characteristics of randomized patients (ITT population)

Characteristic		Saxagliptin (N=8280)	Placebo (N=8212)
Age (years)[a]	Mean (SD)	65.1 (8.5)	65.0 (8.6)
	≥65 (n, %)	4290 (51.8)	4271 (52.0)
	≥75 (n, %)	1169 (14.1)	1161 (14.1)
Sex (n,%)	Male	5512 (66.6)	5525 (67.3)
	Female	2768 (33.4)	2687 (32.7)
Race (n, %)	White	6241 (75.4)	6166 (75.1)
	Black/African American	278 (3.4)	290 (3.5)
	Asian	896 (10.8)	884 (10.8)
	Native Hawaiian or Other Pacific	11 (0.1)	11 (0.1)
	American Indian or Alaska Native	18 (0.2)	33 (0.4)
	Multiracial	768 (9.3)	758 (9.2)
	Other	68 (0.8)	70 (0.9)
Weight (kg)[a]	Mean (SD)	87.7 (18.7)	88.1 (19.4)
	≥80 (n, %)	5291 (63.9)	5265 (64.1)
Body mass index (kg/m^2)[a]	Mean (SD)	31.1 (5.5)	31.2 (5.7)
	≥30 (n, %)	4446 (53.7)	4370 (53.2)
Duration of T2DM (years)	Median	10.3	10.3
	Interquartile range	5.2, 16.7	5.3, 16.6
HbA1c (%)	Mean (SD)	8.0 (1.4)	8.0 (1.4)
	Category (n, %)		

Table 1 Demographic and baseline characteristics of randomized patients (ITT population)

Characteristic		Saxagliptin (N=8280)	Placebo (N=8212)
	<6.5	590 (7.1)	673 (8.2)
	6.5 - <7.0	1442 (17.4)	1414 (17.2)
	7.0 - <8.0	2759 (33.3)	2657 (32.4)
	8.0 - <9.0	1577 (19.0)	1562 (19.0)
	≥9	1761 (21.3)	1764 (21.5)
eGFR (mL/min)[b]	Mean (SD)	72.5 (22.6)	72.7 (22.6)
	Category (n, %)		
	>50	6986 (84.4)	6930 (84.4)
	≥30 - ≤50	1122 (13.6)	1118 (13.6)
	<30	172 (2.1)	164 (2.0)
Urinary albumin/creatinine ration (mg/mmol)	Median	1.8	1.9
	Interquartile range	0.7, 7.5	0.7, 7.9
	Category (n, %)		
	<3.4	4867 (58.8)	4829 (58.8)
	≥3.4 - ≤33.9	2217 (26.8)	2209 (26.9)
	>33.9	832 (10.0)	806 (9.8)

The denominator of each percentage is the number of patients in the treatment group.

[a] At randomization.

[b] Estimated GFR using the MDRD formula (Levy et al 2006), calculated as 175 × standardized serum creatinine $^{-1\ 154}$ × age $^{-0\ 203}$ × 1.212 (if black) × 0.742 (if female).

eGFR Estimated glomerular filtration rate; HbA1c Glycosylated hemoglobin; ITT Intention-to-treat; MDRD Modification of Diet in Renal Disease; n, N Number of patients; SD Standard deviation; T2DM Type 2 diabetes mellitus.

The treatment groups were balanced with regard to CV risk factors: the percentages of patients with MRF at baseline were 21.6% versus 21.3% for the saxagliptin and placebo groups, respectively; and the percentages of patients with established CVD at baseline were 78.4% and 78.7% for the saxagliptin and placebo groups, respectively.

Diabetes and CVD medication use at baseline was similar in the 2 treatment groups. Overall, 69.3% of patients were using metformin at baseline, 41.2% were using insulin, 39.9% were using an SU, and 5.9% were using a TZD. Approximately 5% of patients were treated with diet and exercise only at baseline. At baseline, approximately 98% of patients in the study were taking concomitant CVD medications; 61.6% were taking beta blockers and 78.3% were taking statins.

3.2 Cardiovascular endpoints

The results for the SAVOR primary endpoint analysis indicated that saxagliptin, when added to standard of care in patients with T2DM who were at high CV risk, neither reduced nor increased the risk of an event of the primary composite endpoint of CV death, non-fatal MI, or non-fatal ischemic stroke.

3.2.1 Primary and secondary composite endpoints

An overview of the results of the time-to-first-event analyses of the primary and secondary composite endpoints and their individual components is presented in Table 2.

There were 1222 patients with an event in the primary composite efficacy endpoint (613 in the saxagliptin group and 609 in the placebo group). The study achieved the primary safety endpoint of non-inferiority of saxagliptin versus placebo, with a HR of 1.00 (95.1% CI 0.89, 1.12), with an upper CI bound <1.3, as specified in the 2008 FDA guidance. However, the study did not achieve the primary efficacy endpoint of superiority of saxagliptin versus placebo, with a p-value for superiority of 0.986. As a result, the formal statistical testing was stopped but nominal p-values were provided for the purpose of descriptive evaluation of other efficacy analyses.

The HR for each component of the primary composite was consistent with the overall MACE composite endpoint, with 95% CIs that included 1.0.

For the secondary composite endpoint of non-fatal MI, non-fatal ischemic stroke, CV death, or hHF, hospitalization for unstable angina, or hospitalization for coronary revascularization, no significant differences were observed between saxagliptin and placebo (HR 1.02 [95% CI 0.94, 1.11]; nominal p=0.66).

The HR for each component of the secondary composite, which was a prespecified analysis, was consistent with the overall secondary composite endpoint with a 95% CI that included 1.0, with the exception of hHF. The HR for hHF favored placebo (HR 1.27; 95% CI 1.07, 1.51; nominal p-value, 0.007). To further explore the unexpected finding regarding hHF, a series of analyses were performed to provide an in-depth characterization of the clinical presentation of patients with this event and their post-event outcomes and to identify predictors of both absolute and relative risk. A detailed discussion of the results is presented in Section 5.

Table 2 Time to first cardiovascular event for the primary and secondary composite endpoints and individual component endpoints (ITT population)

Efficacy variable	Saxagliptin (N=8280)		Placebo (N=8212)		Hazard ratio (95.1% CI)[a]	P-value[a]
	Patients with events, n (%)	Event rate per 100 patient-years	Patients with events, n (%)	Event rate per 100 patient-years		
Primary composite endpoint[b]	613 (7.4)	3.76	609 (7.4)	3.77	1.00 (0.89, 1.12)	0.986
Secondary composite endpoint[c]	1059 (12.8)	6.72	1034 (12.6)	6.60	1.02 (0.94, 1.11)	0.662
Time-to-event analyses for individual composite components[a]						
CV death	269 (3.2)	1.60	260 (3.2)	1.55	1.03 (0.87, 1.22)	0.718
Non-fatal MI	240 (2.9)	1.46	260 (3.2)	1.60	0.92 (0.77, 1.09)	0.336
Non-fatal ischemic stroke	143 (1.7)	0.87	123 (1.5)	0.75	1.15 (0.91, 1.47)	0.240
Hospitalization for heart failure	289 (3.5)	1.76	228 (2.8)	1.39	1.27 (1.07, 1.51)	0.007
Hospitalization for unstable angina pectoris	97 (1.2)	0.59	81 (1.0)	0.49	1.19 (0.89, 1.61)	0.239
Hospitalization for coronary revascularization	423 (5.1)	2.61	459 (5.6)	2.86	0.92 (0.80, 1.04)	0.187

[a] Time-to-event variables for the individual components were not adjusted for multiplicity. Nominal p-values/CIs are presented for the secondary composite endpoint and all time-to-event variables. The CI for the secondary composite, all-cause mortality, and the individual component endpoints is 95%.

[b] The time to first occurrence of any event in the composite primary endpoint of CV death, non-fatal MI, or non-fatal ischemic stroke.

[c] The time to first occurrence of any event in the composite secondary endpoint of CV death, non-fatal MI, non-fatal ischemic stroke, hospitalization for heart failure, hospitalization for unstable angina pectoris, or hospitalization for coronary revascularization.

CI Confidence interval; CV Cardiovascular; CVD Cardiovascular disease; ITT Intention-to-treat; MI Myocardial infarction.

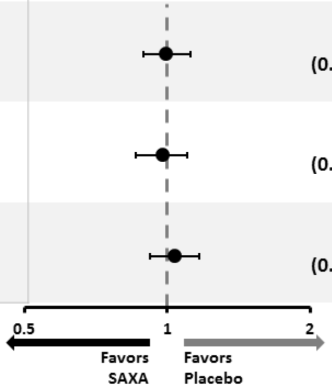
Sensitivity analyses

To test the robustness of the primary (ITT) analysis results, prespecified sensitivity analyses (including analyses based on PP and mITT [on treatment] sets) were done for the primary and secondary composite endpoints. The results were similar to the results of the ITT analyses of the endpoints, and they do not change the interpretation of the overall findings (see Figure 5).

Figure 5 Sensitivity analyses of the primary and secondary composite endpoints

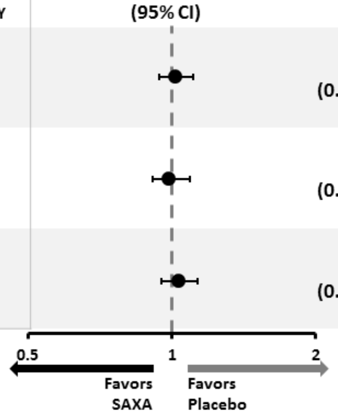
Primary composite endpoint

	SAXA		Placebo		Hazard Ratio (95% CI)
	Patients With Events	Event Rate /100 PY	Patients With Events	Event Rate /100 PY	
ITT	613/8280	3.76	609/8212	3.77	1.00 (0.89, 1.12)
PP	525/7526	3.51	529/7373	3.61	0.98 (0.86, 1.10)
mITT	526/8240	3.52	498/8173	3.40	1.04 (0.92, 1.17)



Secondary composite endpoint

	SAXA		Placebo		Hazard Ratio (95% CI)
	Patients With Events	Event Rate /100 PY	Patients With Events	Event Rate /100 PY	
ITT	1059/8280	6.72	1034/8212	6.60	1.02 (0.94, 1.11)
PP	910/7526	6.29	902/7373	6.36	0.99 (0.91, 1.09)
mITT	954/8240	6.60	911/8173	6.40	1.04 (0.95, 1.13)



Nominal p-values for primary composite: ITT, 0.986; PP, 0.686; mITT (on treatment), 0.539.
Nominal p-values for secondary composite: ITT, 0.662; PP, 0.882; mITT (on treatment), 0.443.

All events were adjudicated by an independent CEC.
CI Confidence interval; HR Hazard ratio; ITT Intention-to-treat; mITT Modified intention-to-treat; PP Per protocol; SAXA Saxagliptin.

Subgroup analyses

The results of subgroup analyses based on prespecified baseline CV risk (established CVD or MRF without established CVD), baseline renal function (normal-mild, moderate, or severe), demographics (age, gender, race, regions, baseline number of risk factors, baseline duration of T2DM, and baseline history of HF), baseline use of diabetes medications (including metformin, insulin, SU, TZD, any oral diabetes medication, any other diabetes medication, or no treatment), and baseline use of CVD medications (including but not limited to statins, angiotensin-converting enzyme [ACE] inhibitors/angiotensin II receptor blockers [ARBs] and aspirin) for the primary and secondary composite endpoints and all-cause mortality were generally similar across subgroups and were consistent with the results for the overall study population. It should be noted that the SAVOR study was not intended or powered to provide definitive information about the subgroups examined.

3.2.2 Secondary endpoint: time to all-cause mortality

The analysis of the secondary endpoint of time to all-cause mortality showed a numerical imbalance with more events on saxagliptin, yielding a HR of 1.11 (95% CI 0.96, 1.27; nominal p=0.154). This numerical imbalance has been further explored in Section 4.

3.3 Other efficacy variables

3.3.1 Diabetic complications

With regard to laser treatment for diabetic retinopathy, other local treatment for diabetic retinopathy, peripheral revascularization, and amputation, no significant differences were found (ie, the 95% CIs for the HRs all included 1.0). However, the numbers of patients with these events may be too small to make meaningful conclusions, and it should be noted that this study was not intended to be a microvascular outcomes study.

3.3.2 Renal disease progression

The event rates for all time-to-event renal disease progression endpoints, including doubling of serum creatinine levels; initiation of chronic dialysis and/or renal transplant and/or serum creatinine >6.0 mg/dL; and composite endpoint of death, doubling of serum creatinine, initiation of chronic dialysis, renal transplant, or serum creatinine >6.0 mg/dL were similar for both treatment groups, with HR 95% CIs that included 1.0.

Data from SAVOR show that saxagliptin reduced the progression of microalbuminuria. From baseline to EoT, fewer patients in the saxagliptin group compared with placebo progressed from normoalbuminuria to microalbuminuria (14.8% vs 16.9%; difference vs placebo of -2.1% [95% CI -3.8%, -0.5%; nominal p-value 0.013]), or from microalbuminuria to macroalbuminuria (11.6% vs 16.5%; difference vs placebo of -4.9% [95% CI -7.4%, -2.5%; nominal p-value <0.001]). The same pattern was observed at 1 and 2 years.

3.4 Summary and conclusions on efficacy in SAVOR

- SAVOR met randomization targets for region, CV risk categories, and renal function. These characteristics were evenly distributed between the 2 treatment groups, providing an appropriate study population for assessment of CV risk in T2DM patients, including patients ≥65 years of age and the ≥75 years of age. More than 200 patients with moderate renal impairment and more than 100 patients with severe renal impairment received saxagliptin for over a year, thus representing a high-risk subgroup of T2DM patients.

- Saxagliptin achieved the primary safety endpoint of non-inferiority versus placebo demonstrating no increased risk of the primary composite endpoint of CV death, non-fatal MI, or non-fatal ischemic stroke (HR 1.00; 95.1% CI 0.89, 1.12). However, SAVOR did not achieve the primary efficacy endpoint of superiority of saxagliptin versus placebo.

- No increased risk of the secondary composite endpoint of CV death, non-fatal MI, non-fatal ischemic stroke, hHF, hospitalization for unstable angina pectoris, or hospitalization for coronary revascularization was observed for saxagliptin versus placebo with a HR of 1.02 and a CI including 1.0 (95% CI 0.94, 1.11), thus supporting the primary non-inferiority safety analysis.

- The SAVOR data showed a numerical imbalance for all-cause mortality with more events on saxagliptin (HR 1.11; 95% CI 0.96, 1.27; nominal p-value, 0.154).

- An increased risk for hHF was observed in the saxagliptin treatment group compared to the placebo group (HR 1.27; 95% CI 1.07, 1.51; nominal p-value, 0.007).

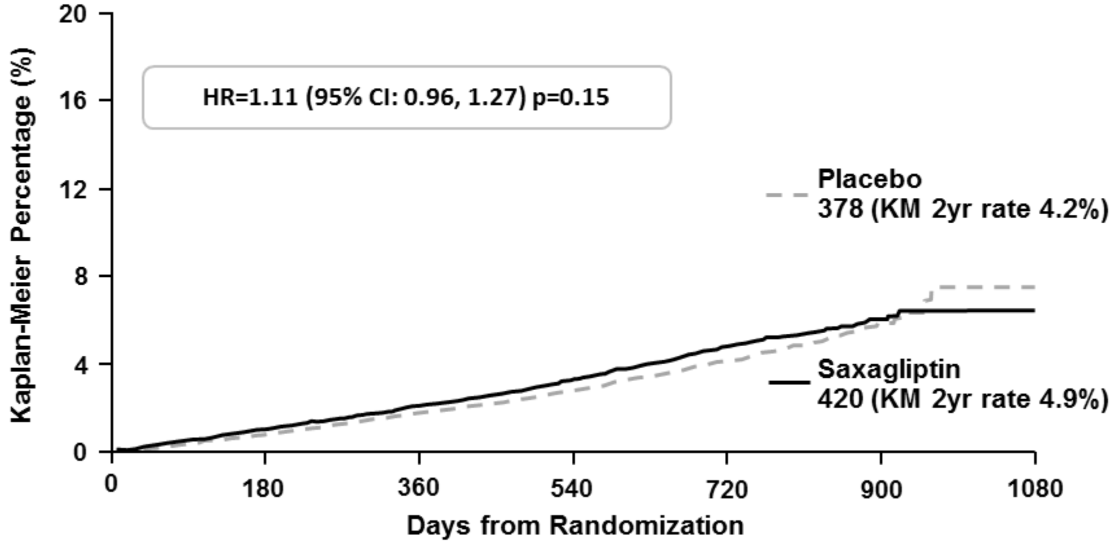
- Saxagliptin did not adversely affect progression of renal disease. Progression of microalbuminuria was reduced with saxagliptin treatment.

The observations on all-cause mortality and hHF are explored in detail in Sections 4 and 5, respectively.

4. SAVOR: ALL-CAUSE MORTALITY DATA

As shown in Section 3.2.2, there was a numerical imbalance in all-cause mortality with more events on saxagliptin (nominal p=0.154). Figure 6 shows Kaplan-Meier estimates of the cumulative percent of time to all-cause mortality.

Figure 6 **Kaplan-Meier estimate of cumulative percent of time to all-cause mortality (ITT population)**



Number of Patients at Risk

Saxagliptin	8280	8182	8070	7636	5181	906	1
Placebo	8212	8134	8032	7615	5152	902	2

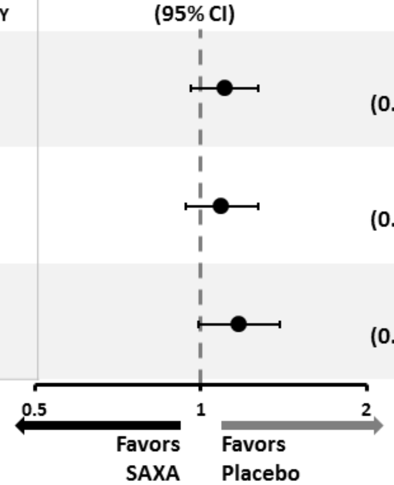
All events were adjudicated by an independent CEC.
CI Confidence interval; HR Hazard ratio; ITT Intention-to-treat; N Number.

To test the robustness of the primary (ITT) analysis results, sensitivity analyses were conducted for the secondary endpoint of all-cause mortality using the PP and mITT (on treatment) analysis populations in SAVOR (Figure 7) (see definitions for analysis populations in Section 2.1.3).

The HRs and 95% CIs for the mITT and PP populations were similar to that of the ITT population, with a higher HR based on fewer events for the mITT (on treatment) population.

Figure 7 Forest plot of the hazard ratio of sensitivity analyses for all-cause mortality

	SAXA		Placebo		
	Patients With Events	Event Rate /100 PY	Patients With Events	Event Rate /100 PY	Hazard Ratio (95% CI)
ITT	420/8280	2.50	378/8212	2.26	1.11 (0.96, 1.27)
PP	366/7526	2.39	329/7373	2.18	1.09 (0.94, 1.27)
mITT	297/8240	1.96	248/8173	1.66	1.18 (0.99, 1.39)



Nominal p-values: ITT, 0.154; PP, 0.233; mITT (on treatment), 0.058.
All events were adjudicated by an independent CEC.
CI Confidence interval; ITT Intention-to-treat; mITT Modified intention-to-treat; PP Per protocol; PY Patient-years; SAXA Saxagliptin.

Of note, in the SAVOR study, 18.4% of patients receiving saxagliptin and 20.8% of patients receiving placebo prematurely discontinued study medication, with total exposure of 15,030.2 patient-years and 14,775.1 patient-years for saxagliptin and placebo, respectively (see Section 3.1.1). Nevertheless, the primary endpoint data are available for all but 2.4% of patients and vital status is available for all but 0.9% of patients. The mITT (on treatment) analysis excluded approximately 32% of all-cause mortality events. This led to a greater probability of placebo events being excluded from the mITT analysis compared with saxagliptin events with attrition bias. This, in combination with generally higher event rates in patients who prematurely discontinued treatment, should be considered in the interpretation of HR using mITT analysis.

4.1 Additional analyses of all-cause mortality

To better understand the nature of the imbalance in all-cause mortality in SAVOR, the following evaluations were performed to explore whether there is any evidence of an increased risk of mortality with saxagliptin treatment. First, an assessment of patient subgroups was conducted to determine if an "at risk" subgroup could be identified. Second, an evaluation of the critical components of all-cause mortality, CV death, and non-CV death was done to determine if a specific type of death or mechanism for death caused by saxagliptin could be identified.

The analysis of the data in the following sections failed to identify an "at risk" subgroup and indicated that there was no excess mortality in SAVOR that was attributable to saxagliptin treatment.

Subgroup analyses of all-cause mortality

Hazard ratio estimates and 95% CIs were used to explore effects within important prespecified subgroups for the secondary endpoint of all-cause mortality. Nominal interaction p-values were reported for descriptive purposes (ie, for the interaction between randomized treatment and the relevant subgroup).

Out of a total of 88 prespecified (per the SAVOR statistical analysis plan) subgroups examined, using a nominal interaction p-value criterion of <0.1 as a conservative approach, a potential treatment interaction was identified for 4 subgroups: patients <65 years, patients from the Asia/Pacific region, patients not taking oral diabetes medications at baseline, and patients not taking any diabetes medications at baseline. The latter 2 subgroups are largely overlapping.

Because these results were not adjusted for multiplicity and due to the large number of subgroups in this large clinical study, some subgroup findings may be due to chance. Additionally, there were some inconsistent results across subgroups and endpoints. For example, with the exception of the observation for age <65 years and ≥65 years, potential interaction findings were not observed consistently across the primary and secondary endpoints (see also Section 3.2). For the primary and both secondary endpoints, including all-cause mortality, the observations in the subgroup based on <65 years and ≥65 years of age were not repeated when the age subgroup was based on age <75 years and ≥75 years. In patients above 65 years, all-cause mortality was balanced with 268 deaths in each treatment group. To explore the <65 age group, additional analyses were conducted by 5-year age groups (Table 3). In the subgroup 55 to 60 years of age, the HR was 2.06 (95% CI 1.33, 3.26). These data show that the relationship with age fluctuates in a manner inconsistent with a true causal relationship with saxagliptin treatment when looking at the age ranges more carefully.

Table 3 Time to all-cause mortality by age group (ITT)

Age group	Total patients	Saxa patients with events	Placebo patients with events	HR (95% CI)
≤40-<45	183	1	5	0.18 (0.01, 1.12)
≤45-<50	469	3	3	0.98 (0.18, 5.32)
≤50-<55	1086	13	15	0.90 (0.42, 1.90)
≤55-<60	2292	62	28	2.05 (1.33, 3.26)
≤60-<65	3900	73	59	1.21 (0.86, 1.71)
≤65-<70	3570	70	86	0.87 (0.63, 1.19)
≤70-<75	2661	84	72	1.15 (0.84, 1.58)
≤75-<80	1798	81	78	1.01 (0.74, 1.38)

CI Confidence interval; HR Hazard ratio; ITT Intention-to-treat.

It is biologically unlikely that saxagliptin would have a higher differential risk in a specific 5-year age group that has balanced baseline characteristics between the treatment groups. With regard to the observed treatment interaction for the Asian region, it is a small group with few fatal events. Finally, although there was an observed interaction with no diabetes medications or no oral diabetes medications at baseline (the subgroups overlap), it is difficult to find an explanation for this finding.

In light of the inconsistency of these findings across endpoints and certain subgroups and the lack of biologic plausibility, these findings could be chance findings and are likely of no clinical relevance from the standpoint of the overall safety of saxagliptin.

4.1.1 Evaluation of CV and non-CV death

Next, an evaluation of the critical components of all-cause mortality, CV death, and non-CV death, was conducted to determine if a specific type of death or mechanism for death could be identified in association with saxagliptin treatment. The investigations described in the following sections did not identify a unifying medical concept to explain the numerical imbalance in mortality observed.

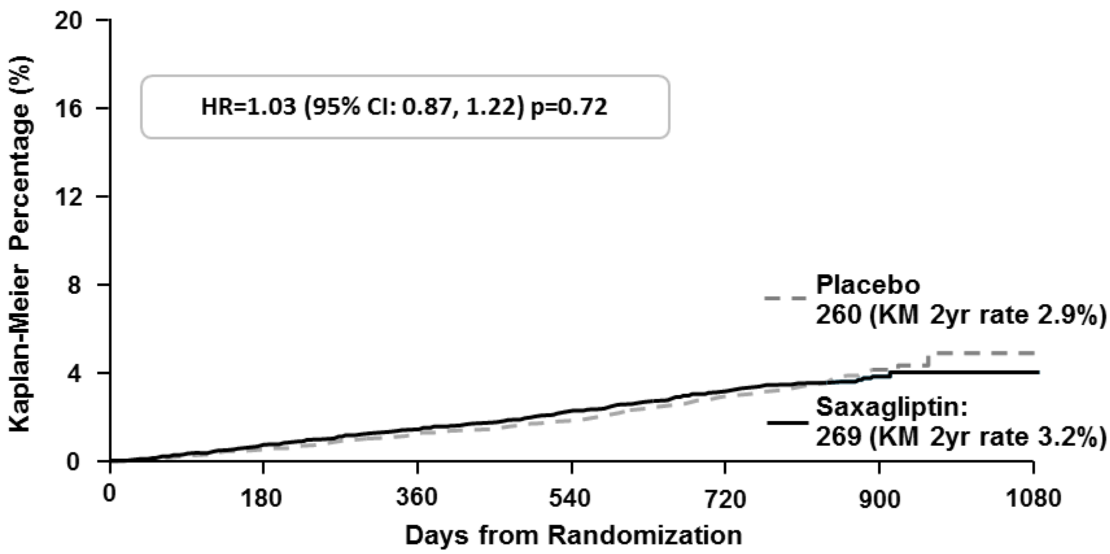
4.1.1.1 CV death

If the numerical imbalance in all-cause mortality was associated with or driven by negative CV effects, an imbalance in the endpoint of CV death might be expected.

A time-to-event analysis of the secondary endpoint component of CV death was a prespecified analysis in SAVOR. Kaplan-Meier estimates of the cumulative percent of time to CV death for saxagliptin and placebo are shown in Figure 8. The HR for the CV death component of the primary composite endpoint was balanced and consistent with the overall MACE (primary) composite endpoint with 95% CIs that included 1.0. The HR for CV death was 1.03

(95% CI 0.87, 1.22). This result indicates that CV deaths were not responsible for the numerical imbalance in all-cause mortality.

Figure 8 Kaplan-Meier estimate of cumulative percent of time to CV death (ITT population)



Number of Patients at Risk

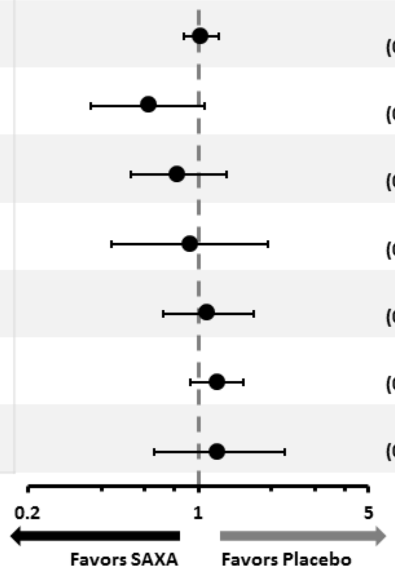
Saxagliptin	8280	8182	8070	7636	5181	906	1
Placebo	8212	8134	8032	7615	5152	902	2

All events were adjudicated by an independent CEC.
CI Confidence interval; CV Cardiovascular; HR Hazard ratio; ITT Intention-to-treat; KM Kaplan-Meier; N Number.

In an analysis of CV death by CV death subcategories, HRs ranged from 0.63 to 1.21, with the lower bound of 95% CIs <1.0 in each case (Figure 9). The endpoint of CV death and the events comprising it were balanced between the saxagliptin and placebo groups, consistent with the primary MACE composite endpoint (primary endpoint); therefore, there is no suggestion of an association of saxagliptin with CV harm.

Figure 9 Forest plot of the hazard ratio for CV death split by reasons of death

	SAXA N=8280		Placebo N=8212		
	Patients With Events	Event Rate /100 PY	Patients With Events	Event Rate /100 PY	Hazard Ratio (95% CI)
Cardiovascular death	269	1.60	260	1.55	1.03 (0.87, 1.22)
Cerebrovascular	22	0.13	35	0.21	0.63 (0.36, 1.06)
Presumed cardiovascular death	35	0.21	42	0.25	0.83 (0.53, 1.31)
Other	14	0.08	15	0.09	0.93 (0.44, 1.93)
Heart failure	44	0.26	40	0.24	1.10 (0.72, 1.69)
Sudden cardiac death	131	0.78	109	0.65	1.20 (0.93, 1.54)
Acute MI	23	0.14	19	0.11	1.21 (0.66, 2.25)



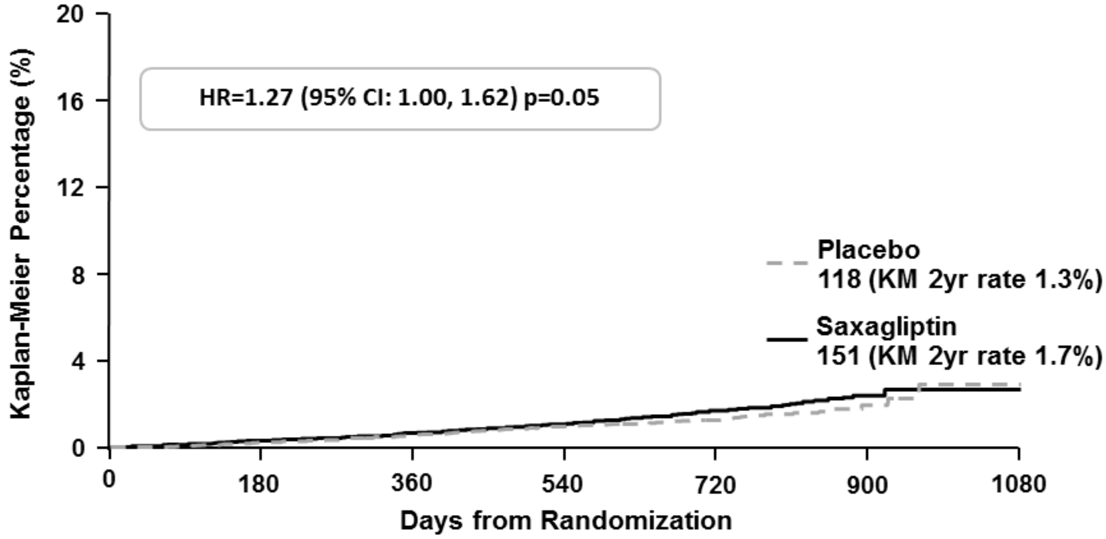
All events were adjudicated by an independent CEC.
CI Confidence interval; CV Cardiovascular; MI Myocardial infarction; PY Patient-years; SAXA Saxagliptin.

4.1.1.2 Non-CV death

Given that CV deaths were balanced across the treatment groups, non-CV deaths were examined to determine the source of the numerical imbalance in all-cause mortality. Whereas all-cause mortality and CV death were evaluated as efficacy endpoints in SAVOR, non-CV death (fatal clinical events adjudicated as non-CV death) was not a prespecified endpoint. This section presents a post-hoc evaluation in the ITT population of events adjudicated by the CEC as non-CV deaths in SAVOR.

Figure 10 shows a Kaplan-Meier estimate of the cumulative percent of patients with time to non-CV death. There was a numerical imbalance in non-CV death, with more events on saxagliptin than placebo (HR 1.27 [95% CI 1.00, 1.62]; nominal p=0.051).

Figure 10 Kaplan-Meier estimates of cumulative percent of time to non-CV death (ITT population)



Number of Patients at Risk

Saxagliptin	8280	8182	8070	7636	5181	906	1
Placebo	8212	8134	8032	7615	5152	902	2

All events were adjudicated by an independent CEC.
CV Cardiovascular; ITT Intention-to-treat; KM Kaplan-Meier.

The adjudicated non-CV death subcategories showed numerical imbalances between treatments, with more fatal events on saxagliptin in the subcategories accident/trauma, hemorrhage, infection, pulmonary failure, and renal failure and more fatal events on placebo in the subcategories malignancy, gastrointestinal causes, and hepatic failure (see Table 4).

The largest subcategory, malignancy, had more events on placebo. The second largest subcategory, with more fatal events on saxagliptin, was infection, with a difference between the treatment groups of approximately 0.2% (Table 4).

Table 4 Causes of adjudicated non-CV death in SAVOR

Cause	Saxagliptin n (%)	Placebo n (%)
Non-CV death	151 (1.82)	118 (1.44)
Malignancy	53 (0.64)	58 (0.71)
Infection	46 (0.56)	28 (0.34)
Pulmonary failure	13 (0.16)	8 (0.10)
Accident	11 (0.13)	5 (0.06)
Renal failure	10 (0.12)	5 (0.06)
Hemorrhage	8 (0.10)	3 (0.04)
Other	5 (0.06)	1 (0.01)
Hepatic	3 (0.04)	4 (0.05)
Gastrointestinal	1 (0.01)	4 (0.05)
Suicide	1 (0.01)	2 (0.02)

HR for the difference between saxagliptin and placebo for non-CV death overall, 1.27 (95% CI 1.00, 1.62; nominal p-value 0.051).
All events were adjudicated by an independent CEC.
CV Cardiovascular.

Further investigation of fatal infections

To further understand whether saxagliptin could be associated with an increase in deaths due to infections, overall events of severe infections, types of infections leading to death, and timing of deaths due to infections were explored. In addition, laboratory data (lymphocyte counts) were examined to determine if saxagliptin was causing an increase in deaths due to infections via decreased lymphocytes. Since saxagliptin treatment may be associated with a decrease in lymphocyte counts that can last up to approximately 3 days after discontinuation of treatment, the timing of the start of infections would likely occur while on or soon after stopping saxagliptin if they were associated with saxagliptin treatment.

Severe infections were included as an AE of special interest (AEOSI) in SAVOR because infections have been seen with saxagliptin and other DPP4 inhibitors and represent a theoretical risk of changes in lymphocytes. Infection was also included the FDA PMR.

Overall, AEs of all infections were balanced between the treatment groups in SAVOR (29.9% in the saxagliptin group and 29.7% in the placebo group). Similarly, severe infections as well as opportunistic infections were balanced between the treatment groups: HR 1.03 (95% CI 0.91, 1.15) and HR 0.61 (95% 0.35, 1.02), respectively (see results for the evaluation of PMR-specified safety topics in Section 6.1.2, Figure 20). The fatal infections in SAVOR were of different types including pneumonia, sepsis, post-procedure infections, and, based on clinical review of the events, many of them were reported in association with other serious events, such as diabetic ulcers, acute gastrointestinal diseases, and post-procedural complications.

Moreover, it is notable that almost half of the infections leading to death started more than a week after discontinuation of study drug.

Laboratory data from the saxagliptin clinical program revealed a reversible, dose-related decrease in absolute lymphocyte count still within normal range. The 10% mean decrease seen in the Phase 2b/3 program was not associated with clinically relevant AEs. Lymphocyte counts in saxagliptin-treated patients reversed back to normal in approximately 3 days after discontinuation of saxagliptin. Lymphocytes from patients in the saxagliptin group who had a decreased lymphocyte count did not exhibit increased rates of apoptosis or necrosis, nor was the rate of lymphocyte proliferation affected. In the SAVOR study, a similar mean change in absolute lymphocyte count from baseline to EoT of -0.064 x 10^9 cells/L from a baseline value of 1.98 x 10^9 cells/L was observed in the saxagliptin group compared to a mean increase of 0.020 x 10^9 cells/L from a baseline value of 1.99 x 10^9 cells/L in the placebo group. The changes were well within the reference range (1.02 to 3.36 x 10^9 cells/L). The proportions of patients with AEs of decreased lymphocyte count were similar between the saxagliptin and placebo groups and AEs of lymphopenia were not reported concurrently with infections. Infections were not the cause of death for 2 patients with low lymphocyte counts who died. Patients who died from infections showed similar fluctuations in lymphocyte counts from baseline in both treatment groups with no overt reduction.

In summary, more patients in the saxagliptin group had fatal events due to infections compared to the placebo group. Given the lack of a temporal relationship to drug for many deaths of infections, the absence of an association with decreased lymphocyte counts, and the fact that overall serious and opportunistic infections were balanced between the treatment groups, a relationship between saxagliptin treatment and infectious death is unlikely.

4.2 Conclusion on all-cause mortality

The numerical imbalance in all-cause mortality was not explained by CV deaths, which were balanced in SAVOR. Non-CV deaths had a numerical imbalance, but a thorough review of the cases failed to identify a unifying medical concept for the non-CV deaths that occurred in the saxagliptin group, making a causal relationship to saxagliptin treatment unlikely. The largest imbalance among the non-CV deaths was in infection deaths, but an examination of these events and associated laboratory data suggested that relationship between saxagliptin treatment and infectious death is unlikely. Therefore, there was no evidence for an increase in mortality attributable to saxagliptin.

5. SAVOR: HOSPITALIZATION FOR HEART FAILURE

In SAVOR, there was an unexpected imbalance with more events of hHF on saxagliptin (nominal p=0.007). Hospitalization for HF was 1 of 6 components of the secondary composite endpoint, as described in Section 3.2.1. For the component of hHF, there was an excess of 61 cases among patients treated with saxagliptin (n=289/8280) versus placebo (n=228/8212). This analysis was prespecified, but was not part of the hierarchical testing to control for multiplicity.

The hHF events occurred throughout the study. Figure 11 shows the Kaplan-Meier estimate of the cumulative percentage of patients with time to first hHF. An imbalance was seen early with a greater risk of hHF among patients treated with saxagliptin. However, the effects of saxagliptin on the risk of hHF were attenuated over time, as evidenced by the HRs from a piecewise Cox regression model.

Figure 11 Kaplan-Meier estimate for adjudicated hospitalization for HF over time in the ITT period in SAVOR

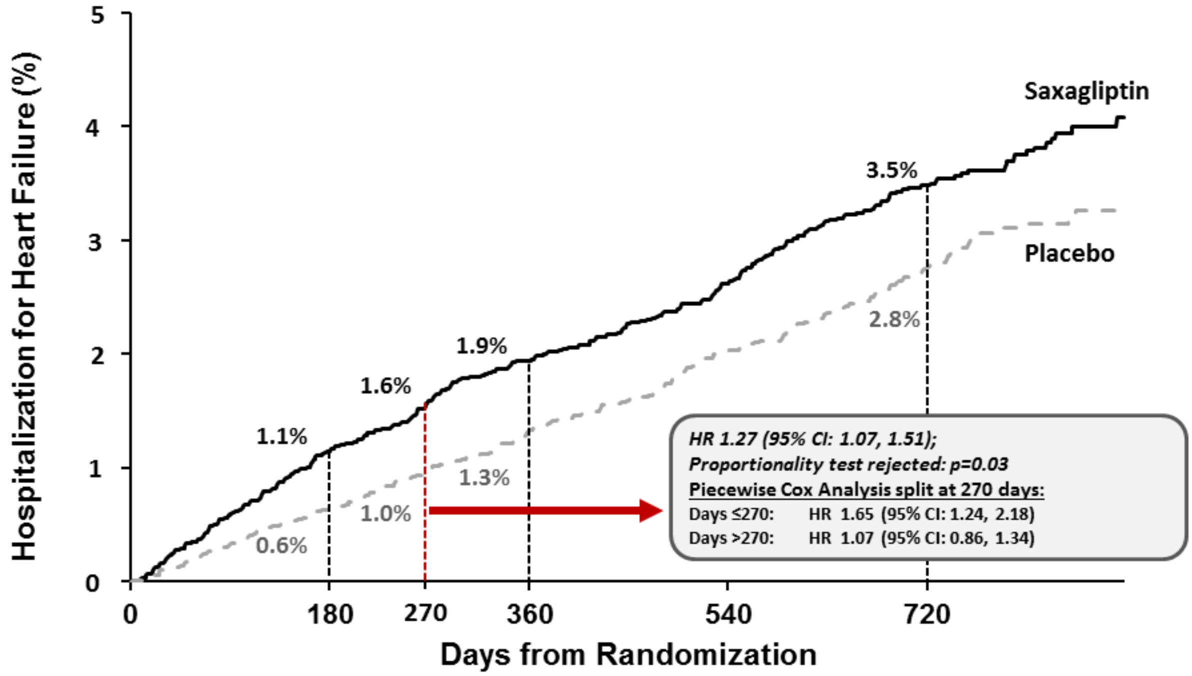


Figure shows time to first occurrence of any hHF. A piecewise Cox proportional hazards model including all data was fit with a change point at 270 days via inclusion of a time dependent covariate in the model. Hazard ratios and 95% CIs before and after the change point were estimated.
CI Confidence interval; HF Heart failure; HR Hazard ratio; ITT Intention-to-treat.

To better understand the observed treatment imbalance for the hHF component endpoint, the Sponsor has conducted a thorough evaluation of data from SAVOR, as well as other available relevant information. This section presents the results of the prespecified exploratory analyses of hHF and post-hoc analyses done to further explore this finding.

Patients experiencing a first hHF were at risk for further HF events and/or death consistent with true hHF events. The proportions were similar for both treatment groups. Among patients treated with saxagliptin, 80/289 (27.7%) experienced at least one recurrent hHF event and 76/289 (26.3%) died. In the placebo group, 57/228 (25.0%) patients had at least one additional hHF and 59/228 (25.9%) died.

5.1 Investigations of hospitalization for HF in SAVOR

The definition of hHF used to adjudicate this event in SAVOR is consistent with the FDA draft guidance provided in the Standardized Definitions for End Point Events in Cardiovascular Trials draft guidance from the FDA (Hicks et al 2010). For a full definition of the hHF endpoint in SAVOR, see Appendix B, Scirica et al 2011 (Appendix B in that publication). Findings based on an analysis of serious adverse events (SAEs) reported by investigators were consistent with the adjudicated analysis of hHF. The HR for investigator-reported Cardiac Failure based on SAEs reported based on narrow Standardized MedDRA Query (SMQ) for Cardiac Failure was 1.18 (95% CI 1.01, 1.39). A similar imbalance between the 2 treatment groups was observed when events were analyzed by broad SMQ terms for Cardiac Failure, but again, restricted to SAEs (HR 1.19 [95% CI 1.01, 1.39]). The concordance between investigator-reported SAE terms for HF and HF events as adjudicated by the CEC is consistent with the conclusion that the events described are events of HF. Therefore, the finding is unlikely to be related to differences in treatment practices that may result in patients with true HF not meeting the adjudication definition.

The composite of time to first event of hHF or CV death is an accepted endpoint for a HF trial (Zannad et al 2013). SAVOR is not a HF study, and therefore, this composite endpoint was examined in a post-hoc analysis. There were 493 events (289 events of hHF and 204 events of CV death) among the 8280 patients treated with saxagliptin and 432 events (228 events of hHF and 204 events of CV death) among the 8212 patients treated with placebo. The HR is 1.14 (95% CI 1.01, 1.30; p=0.041). The excess 61 events are entirely attributable to the component of hHF. The endpoint of CV death is completely balanced across the 2 treatment groups in this analysis (204 events of CV death in each treatment group).

In order to characterize the nature of the hHF events in SAVOR and their relationship to therapy, the following questions were addressed: 1) Is there any other evidence for myocardial injury or HF in association with saxagliptin treatment apart from SAVOR? 2) Are the baseline characteristics, clinical presentation, and clinical course for patients with hHF different in patients treated with saxagliptin versus placebo? 3) Are there risk factors that would predispose a patient to hHF with saxagliptin versus placebo? 4) What other factors have been considered as potential mechanisms for an imbalance in hHF events between the treatment arms? 5) Was there any adverse effect on the primary or secondary endpoints (including all-cause mortality) in those patients at greatest risk for hHF? And finally, 6) How should patients at risk for hHF be managed?

The data show that treatment with saxagliptin was associated with an increased risk for hHF. This finding was most relevant for patients at increased risk for HF such as those with a history of HF or renal impairment and is manageable in the context of the routine care of patients at risk for HF.

5.1.1 Question 1: Is there any other evidence for myocardial injury or HF in association with saxagliptin treatment apart from SAVOR?

Preclinical data pertaining to risk of HF

As a part of the standard drug development process, the potential for saxagliptin to induce adverse CV changes was evaluated using in vitro and in vivo assessments. Saxagliptin was evaluated in vitro for the potential to antagonize the binding of appropriate radioligands to 42 receptors and ion channels, and inhibit 11 different enzymes. No significant effects were observed (<25% inhibition at 10 μM) on the receptors, ion channels, or enzymes evaluated. A single-dose oral telemetry study in dogs did not indicate any saxagliptin-related hemodynamic, conduction, or contractility (assessed via the index of the initial velocity of myocardial contraction dP/dt) changes at maximum plasma concentration exposures 125 times over that in humans at 5 mg. The most sensitive indicator of cardiac insufficiency in longer-term studies is considered to be an increase in heart weight. There was no evidence of saxagliptin-related increases in heart weight across all the preclinical species evaluated (rat/dog/monkey) at daily oral doses for up to 6 months in rats and 1 year in non-rodents with area-under-the-curve exposures up to 619 and 55 times, respectively, of that in humans at 5 mg. This, in conjunction with no other indication of a direct effect on cardiac contractility or histopathology, supports the assessment that there was no evidence of cardiac insufficiency in the preclinical species.

Clinical development program data pertaining to HF

In the saxagliptin early clinical development program, clinical laboratory investigations of aspartate aminotransferase, lactate dehydrogenase, or creatine kinase (nonspecific blood tests potentially elevated in skeletal or cardiac muscle tissue injury) were examined in an ascending single-dose study in normal healthy volunteers and two 14-day ascending multiple-dose studies, one in normal healthy volunteers and one in patients with T2DM. At doses as high as 400 mg daily, administered for 14 days, no consistent abnormalities in these nonspecific markers of muscle tissue injury were observed.

A pooled analysis based on 20 active- and placebo-controlled Phase 2 and Phase 3 studies (N=9156, of whom 5701 were treated with saxagliptin and 3455 were treated with placebo or active comparator) did not demonstrate an increased risk of 'Cardiac failure' with saxagliptin (Iqbal et al 2014). The patients in these studies were at lower risk of CV events than those studied in SAVOR. 'Cardiac failure' AEs were captured from coded AE terms using the Medical Dictionary of Regulatory Activities (MedDRA), version 15.0, SMQ [narrow] for 'Cardiac Failure'. There were a total of 39 HF events and the IRR (saxagliptin/control) was 0.55 (95% CI 0.27, 1.12). This analysis is limited by its retrospective nature, the small numbers of events, and short duration of clinical follow-up.

Saxagliptin postmarketing surveillance data for HF

No signal for HF had emerged during postmarketing surveillance of the estimated 2,384,850 patients exposed to saxagliptin prior to the SAVOR study. As of the time of preparing this document, there has been no signal for HF based on postmarketing spontaneous reports.

5.1.2 Question 2: Are the baseline characteristics, clinical presentation, and clinical course for patients with hHF different in patients treated with saxagliptin versus placebo?

The baseline characteristics (prespecified) of patients who experienced hHF were generally similar between the 2 treatment groups. This was also true for patients who did not experience hHF. However, baseline characteristics of patients with hHF and patients without hHF appeared to differ as shown in Table 5. Patients hospitalized for HF had a longer mean duration of diabetes and greater impairment of renal function at baseline compared with patients who were not hospitalized for HF. Although the broad SAVOR population represented a high–CV risk population, participants who were hospitalized for HF were also more likely to have established CVD at the time of entry into the study. Consistent with having a more significant cardiac history at baseline, patients who experienced hHF were more likely to be treated with cardiac medications at baseline. These observations are generally consistent with baseline characteristics known to be associated with increasing risk for HF.

Table 5 Selected baseline characteristics for patients hospitalized and not hospitalized for HF in SAVOR (ITT)

Baseline characteristics and history (Prespecified)[a]	hHF		No hHF	
	Saxa (N=289)	**Placebo (228)**	**Saxa (N=7991)**	**Placebo (N=7984)**
Baseline characteristics				
Age categorization (yrs)				
<65	106 (36.7%)	79 (34.6%)	3884 (48.6%)	3862 (48.4%)
≥65	183 (63.3%)	149 (65.4%)	4107 (51.4%)	4122 (51.6%)
Gender				
Female	73 (25.3%)	67 (29.4%)	2695 (33.7%)	2620 (32.8%)
Male	216 (74.7%)	161 (70.6%)	5296 (66.3%)	5364 (67.2%)
Race				
White	244 (84.4%)	180 (78.9%)	5997 (75.0%)	5986 (75.0%)
Region				
North America	114 (39.4%)	90 (39.5%)	2521 (31.5%)	2541 (31.8%)
Latin America	26 (9.0%)	20 (8.8%)	1322 (16.5%)	1343 (16.8%)
Asia/Pacific	22 (7.6%)	18 (7.9%)	763 (9.5%)	750 (9.4%)
Europe	127 (43.9%)	100 (43.9%)	3385 (42.4%)	3350 (42.0%)
Mean duration of T2DM (yrs)	14.4	14.7	11.9	11.8
Mean HbA1c (%)	8.0	8.1	8.0	8.0
Mean MDRD GFR (mL/min)	59.4	59.3	72.9	73.0
Baseline history				
Established CVD	259 (89.6%)	208 (91.2%)	6163 (77.1%)	6195 (77.6%)
Myocardial infarction	163 (56.4%)	119 (52.2%)	2984 (37.3%)	2971 (37.2%)
Atrial fibrillation/flutter	71 (24.6%)	49 (21.5%)	525 (6.6%)	557 (7.0%)
History of HF	124 (42.9%)	102 (44.7%)	932 (11.7%)	947 (11.9%)
Cardiac medications (any)	288 (99.7%)	228 (100.0%)	7854 (98.3%)	7844 (98.2%)
ASA	236 (81.7%)	180 (78.9%)	6013 (75.2%)	5975 (74.8%)
Statins	241 (83.4%)	188 (82.5%)	6241 (78.1%)	6247 (78.2%)
Beta blockers	224 (77.5%)	193 (84.6%)	4877 (61.0%)	4868 (61.0%)
ACE inh/ARB	228 (78.9%)	188 (82.5%)	6250 (78.2%)	6329 (79.3%)

[a] Specified in the SAVOR statistical analysis plan.

ACE Angiotensin-converting enzyme; ARB Angiotensin receptor blocker; ASA Acetylsalicylic acid; CVD Cardiovascular disease; GFR Glomerular filtration rate; HF Heart failure; hHF hospitalization for heart failure; ITT Intention-to-treat; MDRD Modification of Diet in Renal Disease; T2DM Type 2 diabetes mellitus.

Patients with hHF presented with signs and symptoms typical for HF regardless of treatment assignment. The most common symptom in both groups was dyspnea (85.8% saxagliptin vs 91.7% placebo). Most patients with dyspnea had at least 1 additional clinical manifestation at the time of presentation that was suggestive of HF (72.0% saxagliptin vs 78.1% placebo). Additional clinical manifestations reported included pulmonary edema, peripheral edema, elevated jugular venous pressure, orthopnea/paroxysmal nocturnal dyspnea, and/or radiographic evidence of worsening HF.

The hospital course was similar for patients treated with either saxagliptin or placebo. Most patients (88.2% in each group) were treated with intravenous diuretics. Vasodilator therapy was used in 6.2% of saxagliptin-treated patients and in 7.9% of placebo-treated patients. Ultrafiltration/hemodialysis (2.8% and 2.2% for saxagliptin and placebo, respectively) and advanced hemodynamic support (1.7% and 0.9% for saxagliptin and placebo, respectively) were infrequently used. In addition, the initial adjudicated hHF, as analyzed by length of stay, was similar between the 2 treatment groups (median stay 7.0 days in each treatment group).

An investigation of clinical events (CV events as defined by the CEC and investigator-reported SAEs) 14 days prior to or 14 days after the hHF to determine if there were differences in the groups that might help explain the imbalance in hHF did not identify a predisposing factor.

The data addressing question 2 show that the medical history, initial presentation, and hospital course were typical for patients with HF and similar between the saxagliptin and placebo treatment groups.

5.1.3 Question 3: Are there risk factors that would predispose a patient to hHF with saxagliptin versus placebo?

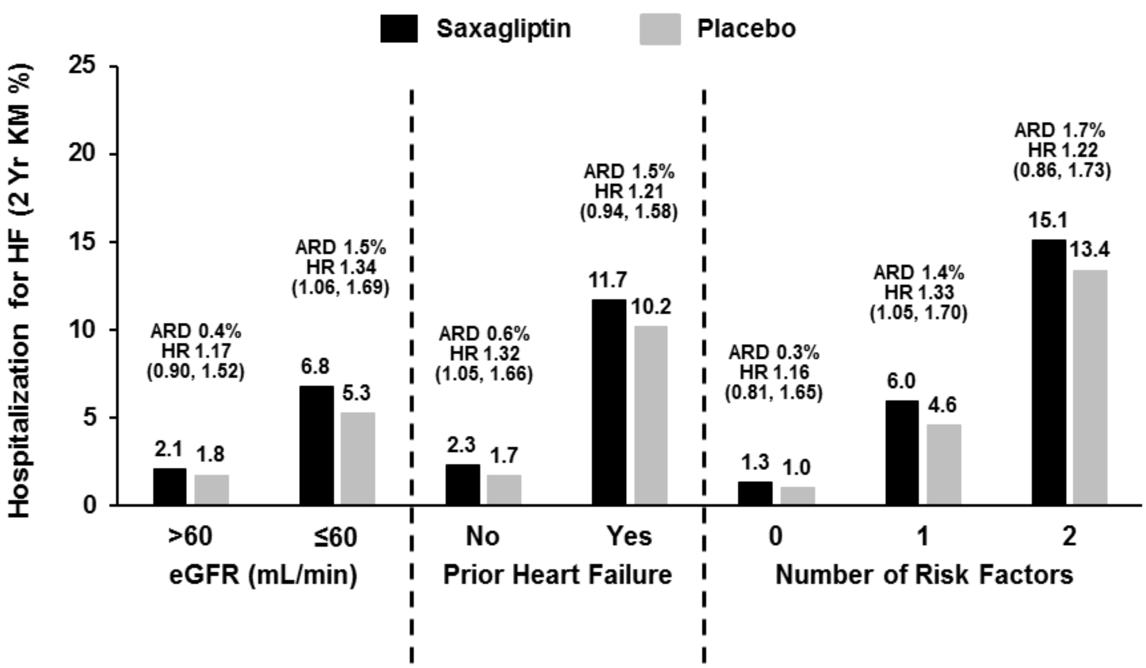
A broad range of baseline factors were examined including prespecified and exploratory variables. They include continuous measures such as age, physical characteristics, vital signs, clinical chemistry and hematology, as well as dichotomous categories, such as medical history (eg, history of coronary artery bypass grafting [CABG]: yes/no) and selected baseline medications usage. Analyses were also performed to determine whether baseline biomarker values are predictive of hHF risk in the study population.

There were no apparent treatment interactions with standard baseline characteristics, such as age, gender, region, body mass index (BMI), vital signs, baseline history of HF, New York Heart Association (NYHA) classification, and baseline eGFR. There were also no apparent treatment interactions with most standard treatments for diabetes and CVD, including ACE inhibitors, with the possible exception of beta blockers and certain hematologic variables (red-cell distribution width [RDW] and neutrophil/lymphocyte distribution ratio [NLR]).

Conventional risk factors

Patients at high absolute risk of hHF irrespective of treatment assignment can be identified by a few conventional risk factors, especially history of HF and renal impairment. These factors have a well-understood causal relationship to HF and patients without either of these factors are at low risk of hHF. There was no evidence of a treatment interaction between these variables. There was a stepwise increase in the risk of hHF in patients who had 0, 1, or 2 of the risk factors of history of HF or an eGFR ≤60 mL/min. Patients with both a history of HF and with significant renal impairment (eGFR≤60 mL/min) were at particularly high absolute risk for hHF while patients with neither of these risk factors appeared to be at a much lower absolute risk of hHF. Approximately 63% of the SAVOR population had a baseline eGFR of >60 mL/min/1.73 m^2 and no history of HF. This group had a particularly low risk of hHF with a 2-year event rate for saxagliptin- and placebo-treated patients of 1.3% and 1.0%, respectively. Patients with both these risk factors represented a small subset of the total SAVOR population and it is for this subgroup of patients that the absolute difference in hHF events is largest. For the 5.4% of the SAVOR population with both of these risk factors, the 2-year event rate for hHF was 15.1% for patients treated with saxagliptin and 13.4% for patients treated with placebo (Figure 12).

Figure 12 Risk of hospitalization for heart failure in patients with and without baseline risk factors (eGFR ≤60 mL/min or history of HF)



ARD calculated based on the difference in event rates per 2-yr KM% and values are round to 1 decimal place.
ARD Absolute risk difference; CV Cardiovascular; eGFR Estimated glomerular filtration rate; HR Hazard ratio.

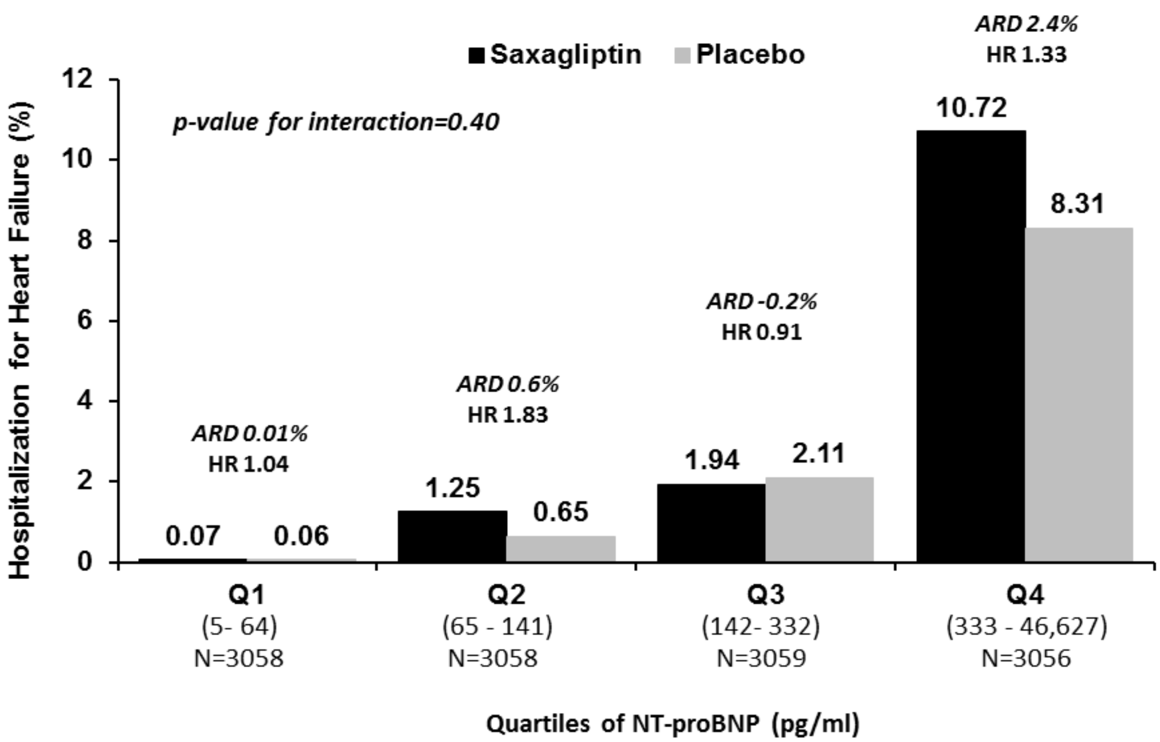
Baseline NT-proBNP

Levels of NT-proBNP are widely used during the care of patients with HF and are of value in diagnosing HF in patients with dyspnea of uncertain etiology as well as in patients at risk for HF such as those with heart disease but without the clinical signs of HF (Braunwald 2013).

Assessing levels of NT-proBNP may be of particular interest as BNP is a substrate for DPP4 in vivo (Usher and Drucker 2012).

Not unexpectedly, given the known association of elevated NT-proBNP with HF risk, patients with baseline NT-proBNP in the highest quartile were at greatest risk for hHF irrespective of treatment assignment (Figure 13). The relative risk with saxagliptin treatment in the highest quartile was similar to that observed in the overall study, with no treatment-by-subgroup interaction observed for baseline NT-proBNP, despite numerical differences in HR across different quartiles (p=0.40; Figure 13).

Figure 13 Risk of hospitalization for HF by baseline NT-proBNP quartile (ITT population)



ARD Absolute risk difference; HR Hazard ratio; NT-proBNP N-terminal prohormone of brain natriuretic peptide; Q Quartile.

5.1.4 Question 4: What other factors have been considered as potential mechanisms for an imbalance in hHF events between the treatment arms?

Play of chance

The evaluation of the data from SAVOR has failed to identify a mechanism that would explain the unexpected increase in hHF. Although the observation could be a play of chance, the nominal p-value of 0.007 on an adjudicated prespecified endpoint makes drawing such a conclusion premature.

Glucose control

Tight control of glucose could potentially contribute to CV side effects in patients who are already at high CV risk, as glucose is an essential metabolic substrate in the myocardium. Associations were therefore explored between hHF and glucose control (HbA1c, including baseline values and response to treatment, and the risk of hypoglycemia). The mean and median baseline fasting plasma glucose, as well as duration of diabetes, were similar in the 2 treatment groups. Additionally, no temporal association between hHF and reported hypoglycemia was identified (6 saxagliptin versus 5 placebo AEs [serious and non-serious] of hypoglycemia within the 14 days prior to hHF).

Additional evidence against hypoglycemia contributing to excess risk for hHF was obtained by examining which baseline characteristics were associated with hypoglycemia in SAVOR and then determining whether these same characteristics were associated with an increased risk of hHF. Baseline use of SUs was the driver of the differential in hypoglycemic events with saxagliptin use. Saxagliptin patients, who at baseline were treated with other antidiabetes medications, including insulin, did not appear to have a higher risk of hypoglycemic events compared to placebo. The HR for hypoglycemia for patients taking SUs at baseline was 1.42 (95% CI 1.25, 1.61), whereas the HR for patients not taking SUs was 1.04 (95% CI 0.95, 1.15). Given this result, if hypoglycemia is driving the excess risk of hHF, then baseline use of SU should be associated with an increased HR for hHF. However, the HRs for hHF were nearly identical for patients with and without SU use at baseline, ie, 1.27 (95% CI 0.93, 1.75) vs 1.28 (95% CI 1.04, 1.58), respectively.

Regarding HbA1c, when this finding was analyzed by prespecified subgroups of baseline HbA1c designed to test any possible relationship of the composite primary and secondary endpoints to ranges of glycemic control, there was no consistent trend. Specifically, HbA1c baseline ranges (<6.5%, ≥6.5 to <7%, ≥7 to <8%, ≥8 to <9% or ≥9%) were reviewed and lower HRs (close to 1) were noted for the HbA1c ranges of ≥7 to <8% and ≥9% ranges, but higher HRs were noted for saxagliptin vs placebo in the <6.5%, ≥6.5 to <7%, and ≥8 to <9% range.

In summary, the totality of evidence does not suggest an association between tight glucose control and hHF risk.

Hematologic variables

Several exploratory hematologic variables (baseline neutrophil and lymphocyte counts, and RDW) were associated with both overall hHF risk as well as a potential treatment interaction with saxagliptin. An association with RDW and prognosis among patients with HF and other CVDs was previously reported by other investigators (O'Meara et al 2006, Felker et al 2007). Increases in RDW, a quantitative measure of anisocytosis, can be due to multiple factors, tend to increase with age, and may be a marker of multiple pathologic processes in patients at risk of hHF (Malandrino et al 2012). Elevations of the NLR are considered to be a marker of inflammation and, in other studies, have been associated with a poor prognosis in decompensated HF and in other CVD states (Uthamalingam et al 2011, Felker et al 2007). Arguing against an inflammatory hypothesis contributing to increased hHF risk, is the finding that elevated hs-CRP, a well-described marker of inflammation and a risk factor in patients with HF, was not associated with increased hHF among patients treated with saxagliptin. The clinical significance of the association with RDW and NLR remains unclear.

Beta blocker use

Approximately 60% of SAVOR patients had recorded use of beta blockers at baseline. Event rates in the beta blocker subgroup were higher than in the non-beta blocker subgroup for both treatment groups. This observation was not unexpected as beta blocker use was greater in patients with known CVD including a baseline history of HF or MI. A potential association between relative risk for hHF and baseline beta blocker treatment was observed: beta blocker use at baseline was associated with lower relative risk for hHF (HR 1.18; 95% CI 0.97, 1.43 vs HR 1.82; 95% CI 1.21, 2.77 in patients with or without baseline beta blockers use, respectively). However, since beta blocker usage is not a randomized factor, it is not clear if this finding is related to beta blocker use or is the result of other factors associated with beta blocker usage, such as the presence of concomitant CV conditions.

Fluid status and hemodynamics

There was no observed imbalance of AEs suggestive of fluid overload, such as edema, peripheral edema, or increased weight.

An analysis of AE terms, including both serious and non-serious events, using the broad SMQ for Cardiac Failure showed that reports of cardiac failure were balanced between the treatment groups (HR 1.02 [95% CI 0.92, 1.13]). In particular, AE reports of edema (45 [0.54%] saxagliptin vs 46 [0.56%] placebo) and peripheral edema (347 [4.19%] saxagliptin vs 352 4.29%] placebo) were balanced with very few SAE reports (5 SAEs total, of which 4 [0.05%] were in the saxagliptin group and 1 [0.01%] among placebo patients). These findings contrast with other classes of diabetes medications, such as TZDs, where edema and fluid accumulation are well-described AEs that may precede the development of HF.

There were small reductions from baseline in mean weight for both males and females in the 2 treatment groups. Mean (standard deviation) changes from baseline to EoT were -0.1 (5.44) kg for males and -0.3 (5.13) kg for females in the saxagliptin group, and -0.1 (5.24) kg for males and -0.4 (5.70) kg for females in the placebo group. No adverse effects on blood pressure or heart rate were observed in the saxagliptin or placebo groups.

While there is no evidence that treatment with saxagliptin results in clinically detectable fluid overload over the course of the study, the extent of supporting data available during the first 6 months of the study is limited, due to the study design. The only data collected during the first 6 months, in addition to data on clinical events, were concomitant medications and study drug compliance. These were collected every 3 months (at each study visit every 6 months and via documented phone calls every 6 months in between study visits) and when an AE was reported. This level of data collection was designed to be optimal for the analysis of the key primary and secondary efficacy and safety endpoints of the study but does not allow for a more in-depth analysis, as vital signs, body weight, and laboratory data were not assessed until the 12-month timepoint.

However, the differential in hHF events occurred early during the SAVOR study and measurements of weights and AEs suggestive of weight gain were collected at later timepoints. If there were early small changes in volume status, perhaps neurohormonally mediated, they could have been missed. Further evaluation of this potential mechanism for the hHF is planned.

Myocyte injury

Several lines of evidence indicate the imbalance in hHF observed in SAVOR was not the result of myocyte injury. First, no signal for myocardial injury was observed in preclinical studies. Second, acknowledging that more patients on saxagliptin vs placebo were hospitalized for HF, treatment with saxagliptin did not increase the risk for subsequent hHF or death compared to placebo. This was in the context of a greater rate of study drug discontinuation among placebo-treated patients. And third, biomarker changes NT-proBNP (a marker of hemodynamic stress), high-sensitivity troponin T (hs TNT; a marker of myocardial necrosis), and high-sensitivity C-reactive protein (hs-CRP; a marker of inflammation) over time are also consistent with the lack of a direct myocardial effect.

Preclinical data pertaining to risk of HF

As described in Section 5.1.1, a comprehensive International Conference on Harmonisation- and Good Laboratory Practice-compliant preclinical program for saxagliptin, with extended duration of dosing in a variety of species, did not identify any adverse CV effects, including HF.

Rate of subsequent events following a first hHF event

Being hospitalized for HF confers an increased risk for subsequent hHF and total mortality (O'Connor et al 2008). Although more patients on saxagliptin vs placebo were hospitalized for HF, randomization to saxagliptin did not appear to increase the risk for those subsequent events among patients in whom the hHF event had already occurred. There were 413 hHF events among the 289 patients treated with saxagliptin versus 328 hHF events among the 228 patients treated with placebo (HR 1.26 [95% CI 1.09, 1.46]; p=0.034), similar to the risk for a first hHF event (HR 1.27 [95% CIs 1.07, 1.51]; p=0.007). The percentage of patients who experienced a subsequent hHF or death appears similar between the saxagliptin and placebo groups (Table 6).

Table 6 Events subsequent to an adjudicated hHF event: rehospitalization for hHF, mortality, and discontinuation of study drug

Subsequent events	Saxagliptin (N=289) n (%)	Placebo (N=228) n (%)
Rehospitalizations for HF	80 (27.7%)	57 (25.0%)
Mortality after HF	77 (26.6%)	60 (26.3%)
Permanent/premature discontinuation of study drug	40 (16.3%)	68 (36.4%)

Discontinuation of active treatment does not explain why, at the level of the individual patient, there was no apparent increase in either the risk of a second hHF or death among patients treated with saxagliptin vs placebo. Among patients hospitalized for HF, discontinuation of study drug occurred more frequently in placebo-treated patients than among those treated with saxagliptin (Table 6). The reasons that were reported for permanent discontinuation were similar between treatment groups; the 3 main reasons were ‘patient decision’, ‘AE/SAE due to investigational product’, and ‘physician choice’.

There is also no evidence that patients treated with saxagliptin had a more complicated course when hospitalized (see Section 5.1.2 above).

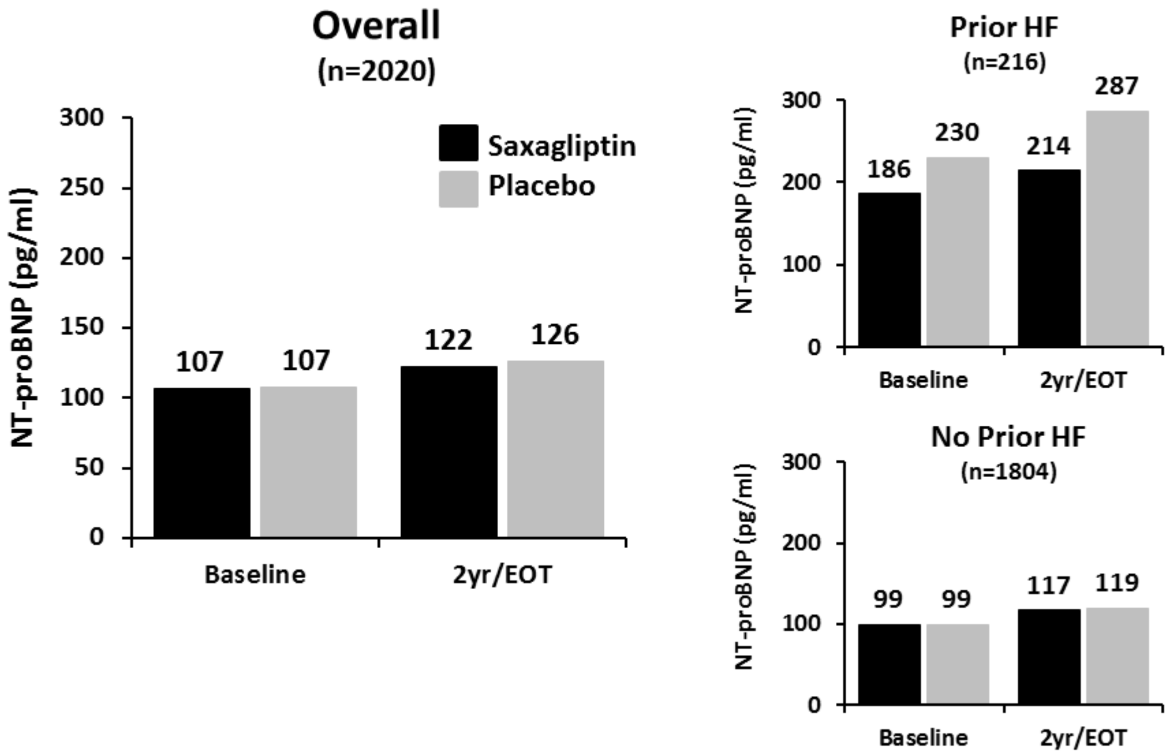
Biomarker findings

Biomarker findings are also consistent with the lack of a direct myocardial effect. Levels of NT-proBNP are widely used during the care of patients with HF as already noted above (see Section 2.1.3). Cardiac-specific troponins have become the most widely used markers of cardiac necrosis in patients with acute coronary syndromes. More recently, elevated circulating levels of cardiac troponins have been described in patients with HF and are associated with a poor prognosis (Braunwald 2013). Pro-inflammatory markers may also be elevated in HF. Elevations of hs-CRP were among the first to be described and are associated with an increased risk of HF (Braunwald 2013).

As part of the prespecified biomarker analysis, a blood sample was to be obtained at baseline and at Year 2/EoT in all randomized patients who consented. Biomarkers were assayed in all available samples from consenting patients at baseline and at Year 2/EoT. Additional random samples were assayed to create a larger set of Year 2/EoT samples for NT-proBNP and hs-TNT to more fully explore whether there might be potential effects of treatment with saxagliptin on these parameters given the hHF observation.

Findings for NT-proBNP are presented in Figure 14, which shows that there was no clinically relevant difference in changes over time between the saxagliptin and placebo groups. For patients with or without a baseline history of HF, there were no clinically relevant differences in changes over time between the saxagliptin and placebo groups.

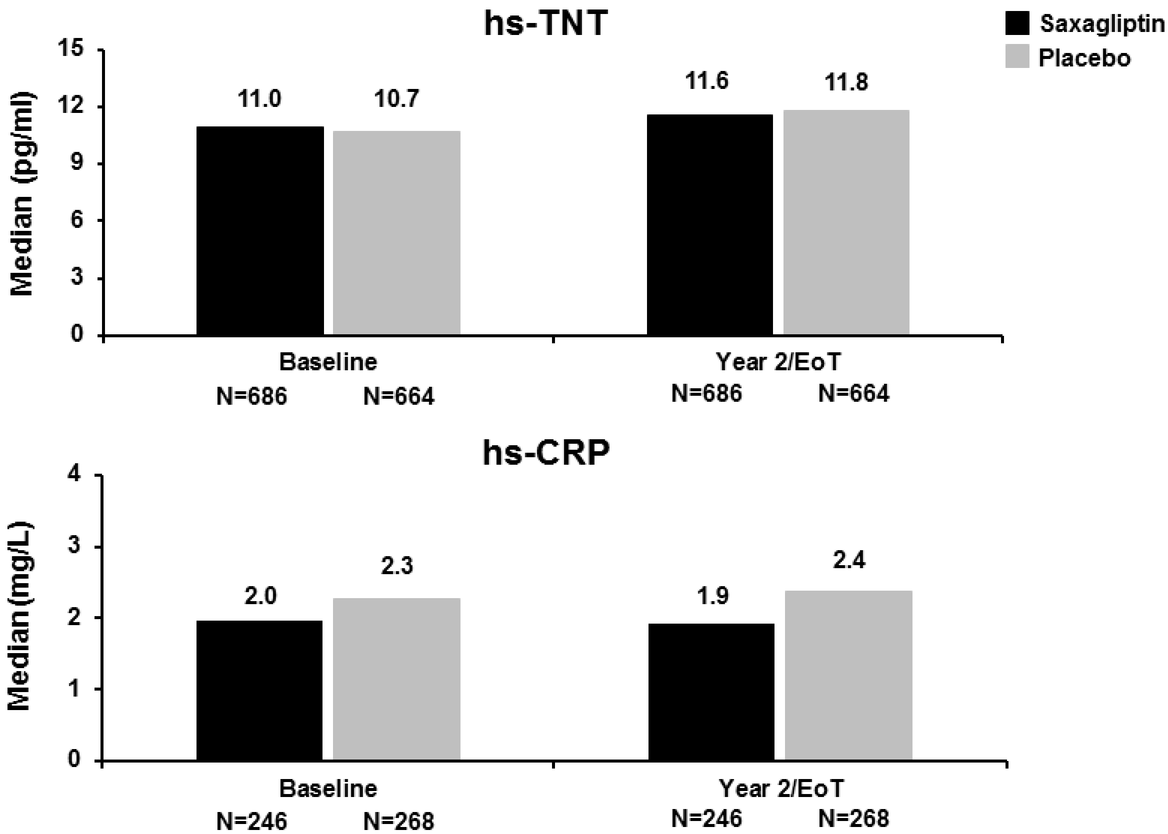
Figure 14 **Change in median NT-proBNP from baseline to year 2/ EoT overall and in patients with or without history of HF**



EoT/Closing Visit was the last visit observation for each patient.
Values shown are medians. Baseline was defined as the last sample taken prior to first dose of study drug (usually Visit 1). Laboratory assessments were taken during and up to 14 days after the last dose of double-blind treatment.
EoT End of treatment; HF Heart failure; ITT Intention-to-treat; NT-proBNP N-terminal prohormone of brain natriuretic peptide.

Similar results were observed for analyses of hs-TNT and hs-CRP. The results of the hs-TNT analysis revealed no relevant differences between the treatment groups for changes from baseline to Year 2/EoT for either hs-TNT (median change from baseline 0.52 and 0.75 for saxagliptin- and placebo-treated patients, respectively) or for hs-CRP (Figure 15).

Figure 15 Median hs-TNT and hs-CRP at baseline and at year 2/EoT (ITT population)



hs-CRP High-sensitivity C-reactive protein; hs-TNT High-sensitivity troponin T.

Results of the ANCOVA analyses of the biomarkers showed that for NT-proBNP, although there were potentially smaller adjusted mean percentage increases from baseline in the saxagliptin group (11% vs 19% in the placebo group, p=0.0380), this difference was not considered to be clinically relevant. For hs-TNT and hs-CRP, there were no clinically relevant differences between the 2 treatment groups in the adjusted mean percentage changes from baseline (hs-TNT [6% vs 9% for saxagliptin and placebo, respectively; p=0.0867]; hs-CRP [7% and 12% for saxagliptin and placebo, respectively; p=0.5710]). (See methods for biomarker analyses in Section 2.1.3).

Threshold analyses were performed in patients who had both baseline and Year 2/EoT biomarker measurements (NT-pro-BNP, hs-TNT, and hs-CRP) to determine how many subjects in the saxagliptin and placebo groups had increases in biomarkers by 25%, 50%, and 100%. Overall, the percentage of patients who exceeded the thresholds of 25%, 50%, and 100% increases were similar between the 2 treatment groups.

In summary, the evidence does not suggest that treatment with saxagliptin causes myocardial injury.

5.1.5 Question 5: Was there any adverse effect on the primary or secondary endpoints (including all-cause mortality) in those patients at greatest risk for hHF?

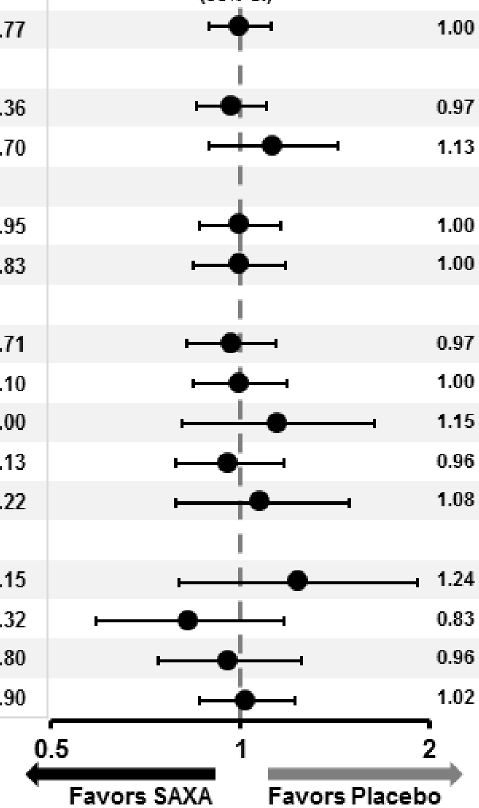
Patients with risk factors for hHF had higher overall event rates for both the primary and secondary endpoints versus patients without such a history, regardless of treatment assignment. However, the imbalance in the frequency of hHF did not preclude the overall balanced HRs for the primary composite endpoint, the secondary composite endpoints, as well as the secondary endpoint of all-cause mortality. A baseline history of HF was a prespecified subgroup of interest for hHF in SAVOR, which included analyses of the primary endpoint, secondary composite endpoint, and secondary endpoint of all-cause mortality by baseline history of HF (Figure 16, Figure 17, and Figure 18, respectively). No treatment interactions were found with baseline history of HF. In other words, there was no evidence of different HRs in this subgroup compared with the overall SAVOR study population.

Hazard ratios for the primary composite endpoint and the secondary composite endpoint were also balanced between the treatment groups for patients with renal impairment (eGFR ≤60 mL/min), patients with both renal impairment and a history of HF, and patients in the top quartile of NT-proBNP.

In the context of an increase in hHF, it is particularly important to emphasize that there is no evidence that high-risk patients treated with saxagliptin experienced an increase in all-cause mortality versus patients treated with placebo (Figure 18).

Figure 16 Primary composite endpoint in patients at high risk for HF

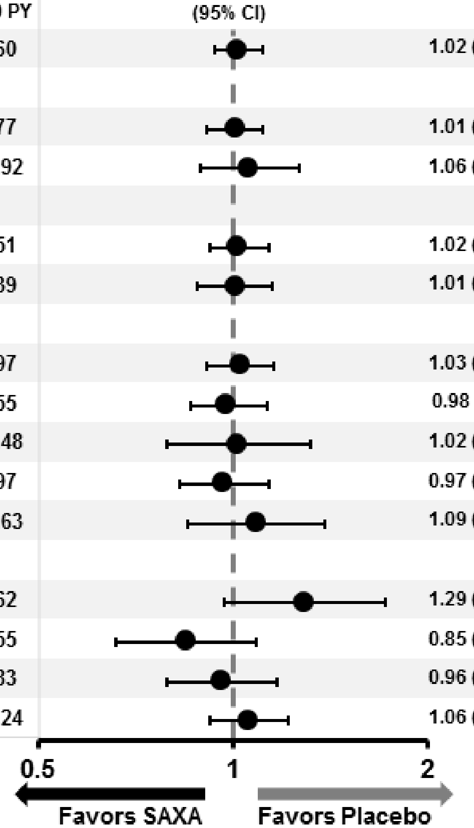
	SAXA		Placebo			
	Patients With Events	Event Rate /100 PY	Patients With Events	Event Rate /100 PY	Hazard Ratio (95% CI)	Interaction p-value
Overall	613/8280	3.76	609/8212	3.77	1.00 (0.89, 1.12)	
Prior History of HF						
No	465/7223	3.24	477/7162	3.36	0.97 (0.85, 1.10)	0.281
Yes	148/1056	7.53	132/1049	6.70	1.13 (0.89, 1.43)	
Renal Impairment (eGFR ≤60)						
No	340/5830	2.92	340/5807	2.95	1.00 (0.86, 1.16)	0.994
Yes	273/2450	5.87	269/2405	5.83	1.00 (0.84, 1.18)	
Combined Risk Factors (HF and eGFR)						
0	274/5227	2.61	281/5191	2.71	0.97 (0.82, 1.14)	0.825
1	257/2600	5.16	255/2588	5.10	1.00 (0.84, 1.19)	
HF only	66/603	5.75	59/616	5.00	1.15 (0.81, 1.64)	
Renal Impairment Only	191/1997	4.98	196/1972	5.13	0.96 (0.79, 1.17)	
2	82/453	10.02	73/433	9.22	1.08 (0.79, 1.49)	
NT-proBNP						
1st Quartile	44/1508	1.40	37/1550	1.15	1.24 (0.80, 1.92)	0.543
2nd Quartile	59/1524	1.90	72/1534	2.32	0.83 (0.59, 1.17)	
3rd Quartile	112/1544	3.68	113/1515	3.80	0.96 (0.74, 1.25)	
4th Quartile	256/1539	9.12	248/1517	8.90	1.02 (0.86, 1.22)	



HF Heart failure; eGFR Estimated glomerular filtration rate; NT-proBNP N-terminal prohormone of brain natriuretic peptide.

Figure 17 Secondary composite endpoint in patients at high risk for HF

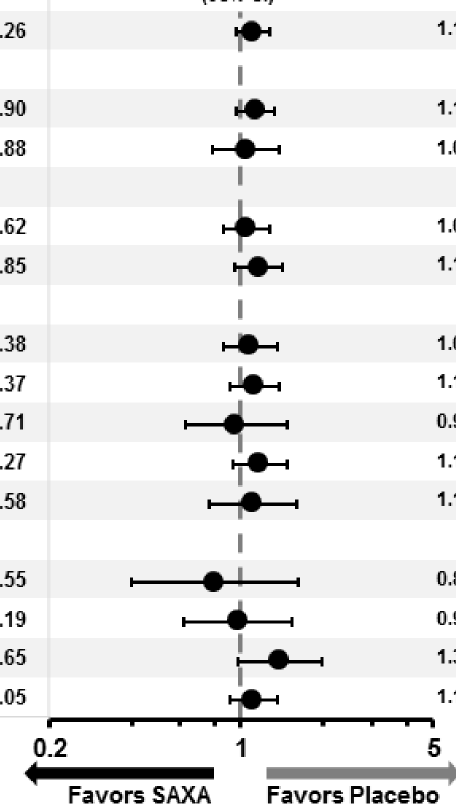
	SAXA		Placebo			
	Patients With Events	Event Rate /100 PY	Patients With Events	Event Rate /100 PY	Hazard Ratio (95% CI)	Interaction p-value
Overall	1059/8280	6.72	1034/8212	6.60	1.02 (0.94, 1.11)	
Prior History of HF						
No	807/7223	5.80	797/7162	5.77	1.01 (0.91, 1.11)	0.632
Yes	252/1056	13.79	237/1049	12.92	1.06 (0.89, 1.27)	
Renal Impairment (eGFR ≤60)						
No	631/5830	5.59	618/5807	5.51	1.02 (0.92, 1.14)	0.850
Yes	428/2450	9.60	416/2405	9.39	1.01 (0.88, 1.15)	
Combined Risk Factors (HF and eGFR)						
0	515/5227	5.04	502/5191	4.97	1.03 (0.91, 1.16)	0.770
1	408/2600	8.52	411/2588	8.55	0.98 (0.86, 1.13)	
HF only	116/603	10.74	116/616	10.48	1.02 (0.79, 1.32)	
Renal Impairment Only	292/1997	7.87	295/1972	7.97	0.97 (0.83, 1.14)	
2	136/453	18.20	121/433	16.63	1.09 (0.85, 1.39)	
NT-proBNP						
1st Quartile	102/1508	3.32	83/1550	2.62	1.29 (0.97, 1.72)	0.160
2nd Quartile	116/1524	3.82	138/1534	4.55	0.85 (0.66, 1.09)	
3rd Quartile	195/1544	6.60	196/1515	6.83	0.96 (0.79, 1.17)	
4th Quartile	397/1539	15.16	374/1517	14.24	1.06 (0.92, 1.22)	



HF Heart failure; eGFR Estimated glomerular filtration rate; NT-proBNP N-terminal prohormone of brain natriuretic peptide.

Figure 18 All-cause mortality in patients at high risk for HF

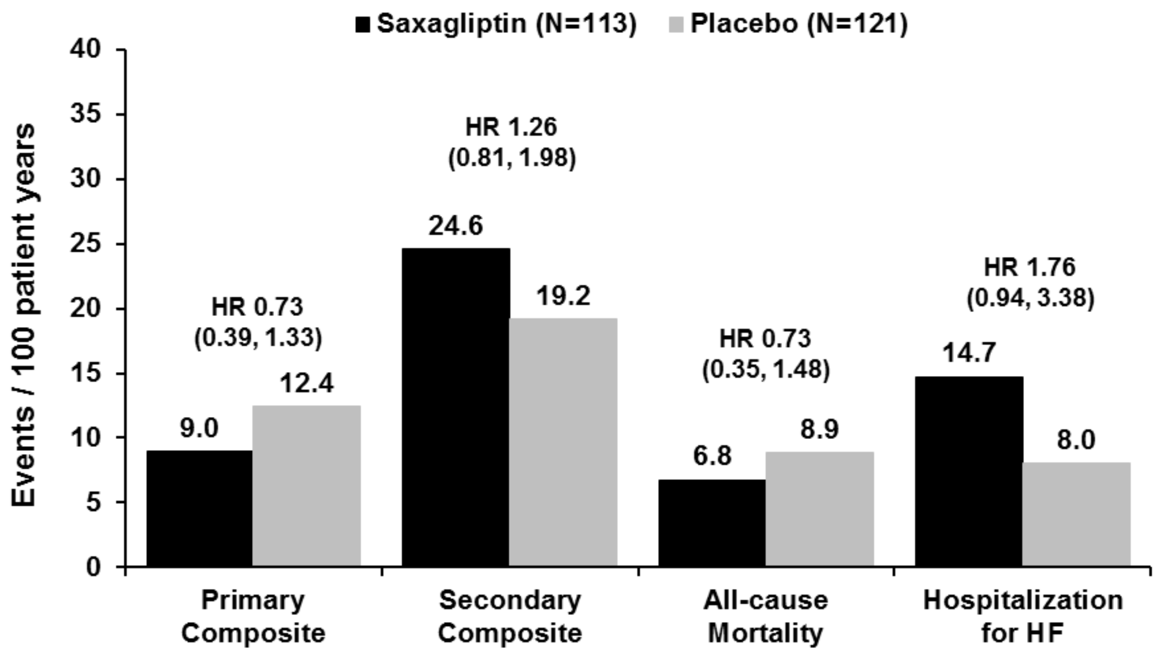
	SAXA		Placebo			
	Patients With Events	Event Rate /100 PY	Patients With Events	Event Rate /100 PY	Hazard Ratio (95% CI)	Interaction p-value
Overall	420/8280	2.50	378/8212	2.26	1.11 (0.96, 1.27)	
Prior History of HF						
No	315/7223	2.14	278/7162	1.90	1.13 (0.96, 1.33)	0.642
Yes	105/1056	5.11	100/1049	4.88	1.05 (0.79, 1.38)	
Renal Impairment (eGFR ≤60)						
No	203/5830	1.70	193/5807	1.62	1.05 (0.86, 1.28)	0.505
Yes	217/2450	4.48	185/2405	3.85	1.16 (0.95, 1.41)	
Combined Risk Factors (HF and eGFR)						
0	161/5227	1.49	148/5191	1.38	1.08 (0.87, 1.36)	0.980
1	196/2600	3.79	175/2588	3.37	1.12 (0.91, 1.37)	
HF only	42/603	3.53	45/616	3.71	0.96 (0.63, 1.47)	
Renal Impairment Only	154/1997	3.87	130/1972	3.27	1.17 (0.93, 1.48)	
2	63/453	7.28	55/433	6.58	1.11 (0.77, 1.60)	
NT-proBNP						
1st Quartile	14/1508	0.44	18/1550	0.55	0.80 (0.40, 1.61)	0.428
2nd Quartile	37/1524	1.17	38/1534	1.19	0.98 (0.62, 1.54)	
3rd Quartile	72/1544	2.29	51/1515	1.65	1.39 (0.97, 1.98)	
4th Quartile	196/1539	6.67	178/1517	6.05	1.11 (0.91, 1.36)	



HF Heart failure; eGFR Estimated glomerular filtration rate; NT-proBNP N-terminal prohormone of brain natriuretic peptide.

Patients with NYHA Class III/IV HF are a subgroup at particularly high risk of hHF and death. In a post-hoc analysis, the Sponsor evaluated the risk for the occurrence of the primary endpoint, secondary composite endpoint, secondary endpoint of all-cause mortality, and hHF according to baseline NYHA Class (Figure 19).

Figure 19 Outcomes in patients with NYHA III/IV HF at baseline



95% CI intervals are shown.
HF Heart failure; HR Hazard ratio. NYHA New York Heart Association.

The imbalance in hHF events is consistent across all patients with a baseline history of HF regardless of baseline NYHA Class (although CIs are wide due to relatively small numbers in each treatment category). As would be expected, patients with more severe HF at baseline experienced higher event rates regardless of treatment assignment. For patients with NYHA Class III/IV HF at baseline, 23.0% (26/113) of saxagliptin-treated patients were hospitalized for HF versus 14.0% (17/121) of those treated with placebo (HR 1.76; 95% CI 0.94, 3.38). Although the point estimate for the HR was increased in this group, there was no indication of a treatment interaction (interaction p-value=0.700).

The data do not suggest that patients with more severe HF at baseline (NYHA Class III/IV) are at increased risk for the occurrence of the primary composite endpoint, secondary composite endpoint, or the secondary endpoint of all-cause mortality when treated with saxagliptin. For the secondary endpoint of all-cause mortality, saxagliptin-treated patients with baseline NYHA Class III/IV HF, had a numerically lower event rate versus placebo-treated patients (event rate of 12.4% [14/113] for saxagliptin versus 16.5% [20/121] for placebo with a HR of 0.73 [95% CI 0.35, 1.48]). Although this analysis is limited by small numbers and wide CIs, treatment with saxagliptin does not appear to increase mortality even in these very sick patients.

5.1.6 Question 6: How should patients at risk for hospitalization for HF be managed?

Irrespective of the choice of antidiabetic therapy, patients at risk for hHF should be managed for signs and symptoms of HF. Based on the data from the SAVOR study, patients experiencing a hHF had a medical history, initial presentation, and hospital course and disposition that were typical for patients with HF and similar for saxagliptin- and placebo-treated patients. Importantly, patients at risk for hHF can be readily identified by the presence of well-recognized risk factors, such as a prior history of HF or renal insufficiency. Given these characteristics, patients at risk for hHF with saxagliptin can be managed using standard practices for the management of patients at risk for HF. No special interventions are necessary. Appropriate communication of the finding of an increased risk for hHF with saxagliptin in the Prescribing Information will enable physicians and other health care providers to identify these patients and to take steps during routine diabetes clinical care to potentially prevent hHF for those at high risk.

5.2 Hospitalization for HF: summary and conclusions

In summary, the finding for hHF was unexpected with no signal for either HF or myocardial toxicity previously seen in the development program. Outside of the SAVOR study, no signal for HF was observed in preclinical studies or clinical studies or through routine pharmacovigilance.

The medical history, initial presentation and hospital course and disposition in patients with a hHF were typical for patients with HF. Patients at risk for HF can be identified using risk factors known to be associated with an increased risk for HF such as a prior history of HF or renal impairment.

The potential etiologies for the hHF finding were explored. No association between hHF and glucose lowering was observed. There was no observed imbalance of AEs suggestive of fluid overload, such as edema, peripheral edema, or increased weight although limitations in study design do not allow definitive conclusions on this potential mechanism. Importantly, several lines of evidence indicate the imbalance in hHF observed in SAVOR was not the result of myocyte injury. First, no signal for myocardial injury was observed in preclinical studies. Second, acknowledging that more patients on saxagliptin vs placebo were hospitalized for HF, treatment with saxagliptin did not increase the risk for subsequent hHF or death compared to placebo. This was in the context of a greater rate of study drug discontinuation among placebo-treated patients. And third, biomarker changes NT-proBNP (a marker of hemodynamic stress), high-sensitivity troponin T (hs-TNT; a marker of myocardial necrosis), and high-sensitivity C-reactive protein (hs-CRP; a marker of inflammation) over time are also consistent with the lack of a direct myocardial effect.

Of note, in the patients at highest risk for hHF, such as those with a prior history of HF, renal insufficiency, elevated NT-proBNP, or New York Heart Association (NYHA) Class III/IV, the effects of treatment on the primary and secondary composite study endpoints and all-cause mortality endpoint were balanced. To better characterize the hHF observation, the Sponsor is implementing the following measures:

- An update to the Risk Management Plan, adding HF as an important potential risk to be evaluated with routine pharmacovigilance, including specific case report form (CRF) pages in clinical studies and targeted questionnaires for spontaneous reports
- A planned clinical study to investigate potential mechanisms that could contribute to this finding
- A planned pharmacoepidemiologic study to investigate whether treatment with saxagliptin is associated with an increased risk in the development of HF in real world use

The Sponsor will also be working with the FDA to ensure the appropriate inclusion of the findings from SAVOR into the Prescribing Information.

To summarize, in SAVOR, an association between saxagliptin treatment and an increased risk for hHF was observed; however, a mechanism to account for the hHF finding in SAVOR has yet to be determined. Patients with easily assessed clinical risk factors, such as a history of HF or renal impairment, are at high absolute risk, while patients without these risk factors appeared to be at much lower absolute risk. Thus, given the characteristics of the finding, focused clinical attention to patients at greatest risk for the development of HF is likely to decrease the possibility of hHF occurring in patients on saxagliptin.

6. SAVOR: CLINICAL SAFETY RESULTS

The safety data from SAVOR have added substantially to the overall body of clinical information on saxagliptin, which together with nonclinical, Phase 2b/3/3b clinical, and postmarketing safety surveillance data provide the evidence base for determining the safety of saxagliptin. Specifically, SAVOR has added saxagliptin exposure and safety data in an older population (4265 patients ≥65 years of age, of whom 1160 patients ≥75 years of age) with a longer duration of T2DM and MRF for, or established, CVD, as well as in patients with moderate (1117 patients) or severe (170 patients) renal impairment. Overall, the results of SAVOR have provided reassurance regarding the safety and tolerability profile of saxagliptin in patients with T2DM.

6.1 Adverse events

6.1.1 Overview of adverse events

AEs that occurred during SAVOR are summarized by category in Table 7.

The proportion of patients with at least 1 AE (including hypoglycemia) was similar between the saxagliptin and placebo groups (73.7% and 73.6%, respectively). More saxagliptin-treated patients than placebo-treated patients had at least 1 AE reported by the investigator to be treatment-related (895 [10.8%] vs 788 [9.6%] patients). The proportion of patients with SAEs reported by the investigator to be treatment-related was low in both treatment groups (58 [0.7%] patients in the saxagliptin group and 40 [0.5%] patients in the placebo group).

The most frequently reported AEs leading to discontinuation of study drug (preferred term [PT] frequency ≥0.2% in either treatment group) were nausea (0.4% and 0.2% of patients in the saxagliptin and placebo groups, respectively), diarrhea (0.3% and 0.3%, respectively), dizziness (0.2% and 0.2%, respectively), headache (0.2% and 0.1%, respectively), and abdominal pain (0.2% and <0.1%, respectively).

When stratified by baseline CV risk categories, the trends observed for SAEs and AEs leading to discontinuation of study drug were consistent with those seen for all AEs.

Table 7 Overall summary of adverse events (ITT population)

Adverse event[a]	Number (%) of patients	
	Saxagliptin (N=8280)[b]	Placebo (N=8212)[b]
Number of patients with:		
At least 1 AE	6100 (73.7)	6046 (73.6)
At least 1 drug-related AE	895 (10.8)	788 (9.6)
At least 1 SAE	2148 (25.9)	2095 (25.5)
At least 1 drug-related SAE	58 (0.7)	40 (0.5)
Permanently discontinued study drug due to SAE	129 (1.6)	159 (1.9)
Permanently discontinued study drug due to AE	406 (4.9)	410 (5.0)

This table includes hypoglycemic events and excludes adjudication-confirmed CV events and deaths; see Section 3.2 for a detailed presentation of those topics.

a Patients with events in more than one category are counted in each category. Patients with multiple events in the same category are counted only once in that category.

b Includes all patients who were randomized (ITT population), including patients who never took study medication. The AEs included all AEs that occurred on or after date of randomization.

AE Adverse event; CV Cardiovascular; ITT Intention-to-treat; SAE Serious adverse event.

6.1.2 Adverse events of special interest

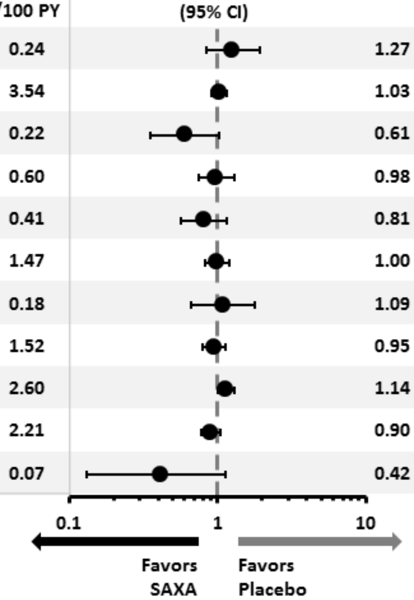
Prespecified AEOSI included decrease in lymphocyte counts, severe infections, opportunistic infections, hypersensitivity reactions, liver abnormalities, bone fractures, skin reactions, pancreatitis, renal abnormalities, cancer, and pancreatic cancer. AEOSI were identified by 3 possible criteria: reported by the investigator as an AEOSI on the CRF, by searching the full database for all PTs matching a prespecified MedDRA list of terms, and/or by meeting prespecified laboratory criteria. The multiple sources, combination schemes, and populations used to summarize AEOSI findings should be carefully considered when interpreting the data.

Figure 20 displays the HRs for the time to first event for all AEOSI. The data shown represent the overall treatment category of the ITT population; results for the ITT and on-treatment analyses were generally similar.

The occurrence of prespecified AEOSI was generally balanced between groups. The lower limits of the CIs were less than 1, except for renal abnormalities where the HR was 1.14 with a lower CI limit of 1.0.

Figure 20 Forest plot of hazard ratio for adverse events of special interest (ITT population)

	SAXA N=8280		Placebo N=8212		Hazard Ratio (95% CI)
	Patients With Events	Event Rate /100 PY	Patients With Events	Event Rate /100 PY	
Decrease in lymphocyte count†	50	0.30	39	0.24	1.27 (0.84, 1.94)
Severe infections‡	585	3.63	567	3.54	1.03 (0.91, 1.15)
Opportunistic infections‡	22	0.13	36	0.22	0.61 (0.35, 1.02)
Hypersensitivity reactions‡	98	0.59	99	0.60	0.98 (0.74, 1.30)
Liver abnormalities†	55	0.33	67	0.41	0.81 (0.57, 1.16)
Bone fractures‡	241	1.47	240	1.47	1.00 (0.83, 1.19)
Pancreatitis AEs‡	33	0.20	30	0.18	1.09 (0.66, 1.79)
Skin reactions‡	236	1.44	247	1.52	0.95 (0.79, 1.13)
Renal abnormalities†	481	2.96	421	2.60	1.14 (1.00, 1.30)
Cancer	326	1.99	359	2.21	0.90 (0.77, 1.05)
Pancreatic cancer	5	0.03	12	0.07	0.42 (0.13, 1.13)



†Case report form, labs, preferred term
‡Case report, preferred term

Events that occurred after study completion were excluded from the analyses.
AE Adverse event; CI Confidence interval; HR Hazard ratio; ITT Intention-to-treat; PY Patient-years; SAXA Saxagliptin.

Renal abnormalities comprised a broad definition, with 3 criteria based on AE reporting, information in the CRF, and laboratory findings. AEs of renal abnormalities occurred in generally similar proportions of patients in the 2 treatment groups across reported PTs, although AEs of acute renal failure were more frequent in the saxagliptin group than in the placebo group. However, a review of cases of renal transplant, initiation of renal dialysis, and creatinine values >2.5 mg/dL showed no difference between the treatment groups. Changes in renal function assessed by serum creatinine and eGFR as safety variables were similar between the saxagliptin and placebo groups. The proportions of patients with predefined marked abnormalities in serum creatinine (>2.5 mg/dL) were also similar between the 2 treatment groups.

Analysis of renal disease progression as an efficacy endpoint (see Section 3.3) showed that fewer patients in the saxagliptin group than in the placebo group progressed in albuminuria and suggested a possible protective effect of saxagliptin. Event rates for all time-to-event renal disease progression endpoints, including a composite endpoint, were similar for both treatment groups (see Section 3.3.2) The numbers of patients who had a doubling of serum creatinine or a serum creatinine level >6 mg/dL were balanced between the groups.

7. SAVOR: GLYCEMIC EFFECTS AND HYPOGLYCEMIA

Although SAVOR was not designed to assess differences between saxagliptin and placebo in measures of glycemic control, exploratory endpoints included annual assessments of HbA1c and the proportions of patients reaching HbA1c target. HbA1c was 0.3% lower in the saxagliptin group than in the placebo group at 1 year, 2 years, and EoT (7.6% versus 7.9%; nominal p<0.001 for all comparisons). Significantly more patients in the saxagliptin group than in the placebo group had an HbA1c level <7% by the end of the treatment period (37% versus 28%; nominal p<0.001).

The improvements in HbA1c and the proportion of patients reaching HbA1c target among saxagliptin-treated patients were observed despite significantly higher rates of upward adjustments in diabetes medications or initiation of new diabetes medications or insulin in the placebo group. Additionally, significantly more patients reached the HbA1c target <7% without hypoglycemia in the saxagliptin group than in the placebo group (31% versus 24%; nominal p<0.001).

The need for new diabetes medication and the need to start an insulin regimen lasting ≥3 months were both higher in the placebo group compared with the saxagliptin group, with 95% CIs that did not include 1.0. Overall, 31.3% of patients in the placebo group started diabetes medications during the study compared with 24.5% of patients in the saxagliptin group (ie, started post-randomization), and 11.0% of patients in the placebo group started an insulin regimen compared with 7.3% of patients in the saxagliptin group.

Assessment of hypoglycemia

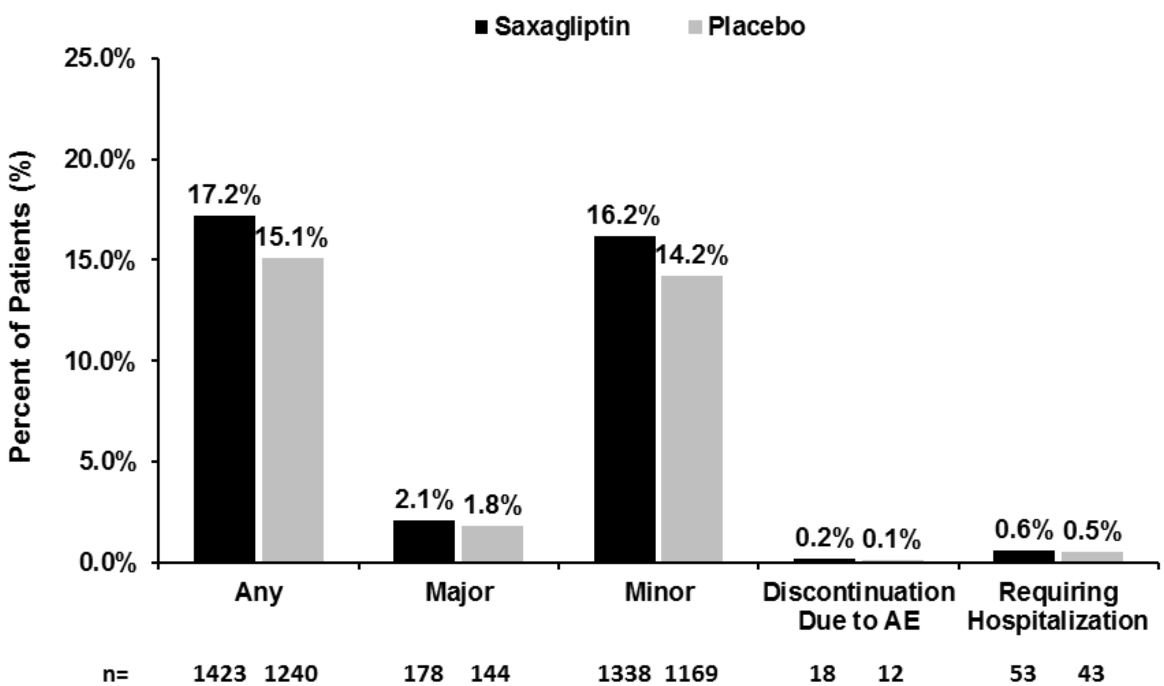
Each patient was provided a diary in which to record symptoms of hypoglycemic episodes and any blood glucose values measured in connection with the episode as well as any value <54 mg/dL (<3.0 mmol/L). A hypoglycemic event could be either an episode with symptoms and confirmed low glucose, an episode with low glucose, or an episode with symptoms when glucose was not measured. Regardless of the presence of any symptoms, any recorded blood glucose <54 mg/dL (<3.0 mmol/L) was to be reported as a hypoglycemic AE.

A hypoglycemic AE was defined as either minor or major. A minor hypoglycemic event was defined as an event where there was an awareness of the event, the event was tolerated, the patient recovered by her/himself, and the event resolved within 30 minutes of ingestion of carbohydrates (if possible, confirmed with a fingerstick value). A measurement of blood glucose <54 mg/dL (<3.0 mmol/L) without symptoms was also considered a minor hypoglycemic AE. A major hypoglycemic event was an event that required the assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions.

Hypoglycemia was reported more frequently in the saxagliptin group than in the placebo group. The increased risk of hypoglycemia was primarily observed in those saxagliptin-treated patients using an SU at baseline. The proportions of patients with AEs and SAEs of hypoglycemia reported by the investigator to be treatment-related were higher in the saxagliptin group compared with the placebo group, although the numbers of events were low in both groups.

Figure 21 displays the proportions of patients in each treatment group with events of hypoglycemia (all, major, minor, leading to discontinuation of study drug, and leading to hospitalization) in the ITT population.

Figure 21 Hypoglycemia events (ITT population)

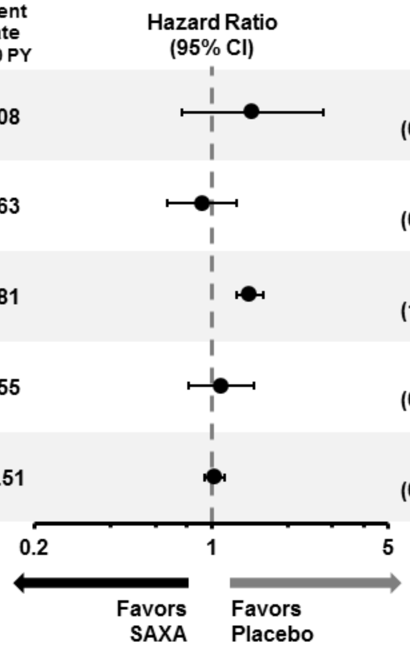


Note: Discontinuation refers to discontinuation of study drug.
AE Adverse event; ITT Intention-to-treat.

As stated in the US Prescribing Information, when saxagliptin is used with an insulin secretagogue (eg, SU) or insulin, a lower dose of insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. In the SAVOR study, the increased risk of hypoglycemia observed in the saxagliptin-treated group occurred primarily in patients treated with an SU (HR 1.42 [95% CI 1.25, 1.61]) at baseline rather than in patients with use of insulin (HR 1.03 [95% CI 0.94, 1.13]) or metformin monotherapy (HR 0.92 [95% CI at baseline 0.67, 1.26]) at baseline (Figure 22).

Figure 22 Hazard ratio of time to first event of any hypoglycemia by baseline antidiabetes medication (ITT)

	Total Subjects	Patients With Events	Event Rate /100 PY	Patients With Events	Event Rate /100 PY	Hazard Ratio (95% CI)
No baseline OAD	787	21	2.97	17	2.08	1.44 (0.76, 2.76)
Metformin alone	3142	76	2.42	81	2.63	0.92 (0.67, 1.26)
Any sulfonylurea	6586	575	9.74	411	6.81	1.42 (1.25, 1.61)
Any thiazolidinediones	970	94	10.28	81	9.55	1.09 (0.81, 1.47)
Any insulin	6787	930	17.14	903	16.51	1.03 (0.94, 1.13)



Data from overall population

Events of first hypoglycemia assessed by case report form or reported preferred term.
CI Confidence interval; ITT Intention-to-treat; OAD Oral antidiabetics; SAXA Saxagliptin.

8. CONCLUSIONS FROM SAVOR

The summary of data from the SAVOR study presented in this briefing document shows that:

- SAVOR was a well-designed and executed study that was conducted in accordance with the 2008 FDA guidance and met the objective of the guidance by demonstrating that therapy with saxagliptin to treat T2DM is not associated with an unacceptable increase in CV risk.

- Saxagliptin therapy did not increase the risk of the composite MACE endpoint of CV death, non-fatal MI, or non-fatal ischemic stroke, meeting the primary safety objective of SAVOR. Additionally, saxagliptin did not increase the risk of an expanded CV composite endpoint, which also included hHF, hospitalization for unstable angina, or hospitalization for coronary revascularization.

- Although a numerical imbalance was observed in all-cause mortality with more events on saxagliptin, CV mortality was balanced. A detailed investigation of the causes of CV and non-CV death indicated that there was no excess mortality attributable to saxagliptin therapy in the SAVOR trial.

- An increased risk for hHF, a component of the balanced secondary endpoint, was observed with saxagliptin treatment. This finding was most relevant for patients at increased risk for HF, such as those with a history of HF or renal impairment, and is manageable in the context of the routine care of patients at risk for HF.

- Use of saxagliptin was not associated with an increased risk of lymphopenia, severe infections, opportunistic infections, hypersensitivity reactions, hepatic dysfunction, bone fractures, pancreatitis, renal dysfunction, cancer, or pancreatic cancer.

- Use of saxagliptin was associated with consistent glucose-lowering benefits along a low risk for hypoglycemia and reductions in microalbuminuria.

9. BENEFIT:RISK PROFILE OF SAXAGLIPTIN

The results of SAVOR, conducted in over 16,000 T2DM patients at high-risk for CV events, add substantially to the Sponsor's understanding of the benefits and risks of saxagliptin therapy. The SAVOR data showed that saxagliptin, when added to existing background diabetes therapy, was not associated with an increased risk for CV death, non-fatal MI, or non-fatal ischemic stroke in T2DM patients at high risk for CVD, thus fulfilling the FDA PMR. The study showed no difference between saxagliptin and placebo on the overall secondary composite endpoint. Additionally, there was no evidence of an increase in mortality attributable to saxagliptin. An increase in hHF with saxagliptin treatment was observed, which was not seen in prior studies. However, with appropriate monitoring, patients with risk factors for hHF can be managed and continue to receive therapy. Including SAVOR, saxagliptin is one of the most intensively studied medications for treatment of T2DM. A total of 27 clinical trials have now been conducted with saxagliptin, enrolling over 27,000 patients, of whom over 15,000 were treated with saxagliptin. The pharmacovigilance database provides significant additional support for the safety of saxagliptin, with data in over 4 million patients since first approval. The clinical trial and pharmacovigilance data provide a large and robust database for the overall assessment of the benefits and risks of saxagliptin and support an overall positive benefit:risk profile when used to treat T2DM.

Safely lowering HbA1c is a major goal when treating T2DM. As an indicator of average glycemia over several months, HbA1c is a strong predictor of diabetes-related complications. Treatments aimed at decreasing HbA1c levels have been associated with a reduced risk of microvascular complications (eg, nephropathy and retinopathy) in patients with T2DM (Skyler et al 2009). The beneficial effects of decreasing HbA1c levels on the rate of CV events are less evident. Although it is well established that good glycemic control plays a key role in reducing diabetes-related complications, current management of glycemia remains inadequate and insufficient numbers of patients achieve glycemic goals. The American

Diabetes Association and European Association for the Study of Diabetes recommend lowering HbA1c to 7.0% in most patients to reduce the incidence of microvascular disease (Inzucchi et al 2012). This was recently supported by the European Society of Cardiology guideline for diabetes and CVD (Rydén et al 2013).

As an oral treatment, saxagliptin effectively lowers HbA1c levels and provides other benefits for T2DM patients. In controlled clinical studies where saxagliptin was studied as monotherapy or as an add-on to other antidiabetic medications, mean HbA1c reductions between 0.4% and 0.8% were observed. In addition, clinically relevant and statistically significant improvements in fasting plasma glucose and 2-hour postprandial glucose following a standard oral glucose tolerance test were present. The reductions in HbA1c were seen across subgroups regardless of gender, age, race, and baseline BMI. Importantly, saxagliptin treatment was not associated with significant changes in body weight or fasting serum lipids compared to placebo. Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes (Cryer 2014). The fact that saxagliptin also had a low risk for hypoglycemia is also extremely important to patients because of the risks associated with hypoglycemia, especially in highly vulnerable patient populations, such as the ones enrolled in the SAVOR study.

Although the SAVOR study was not designed as a glycemic efficacy study, saxagliptin was associated with significantly improved glycemic control despite higher rates of adjustment in other diabetes medications in the placebo group. Specifically, significantly more patients in the saxagliptin group than in the placebo group had an HbA1c level of <7% by the end of the study, supporting the consistent glycemic benefits with low risk of hypoglycemia observed with saxagliptin across the Phase 2b/3 program. SAVOR also provided important positive information on several AEOSI that are considered potential risks when using saxagliptin or other medications to treat T2DM. In addition to not being associated with an unacceptable risk from the standpoint of MACE, saxagliptin was shown to have a low risk for pancreatitis, bone fractures, infections, malignancy, and renal or liver abnormalities, which is an advantage over some of the other antidiabetic medications.

All medications have risks, and risks have been associated with the use of saxagliptin. Risks currently identified in the ONGLYZA® USPI are the potential for hypoglycemia and hypersensitivity reactions. The risk for hypoglycemia may increase when saxagliptin is used concomitantly with a SU or insulin. It can be managed by lowering the dose of the insulin secretagogue or insulin. Hypersensitivity reactions have been reported postmarketing. If a serious hypersensitivity reaction is suspected, saxagliptin should be discontinued and other potential causes assessed.

In SAVOR, an association between saxagliptin treatment and hHF was observed. This is a new potential risk. The finding was most relevant for patients already at risk for a hHF, such as T2DM patients with a prior history of HF or with renal insufficiency. Importantly, the evidence suggests that saxagliptin does not cause myocardial injury and in those patients at greatest risk for a hHF, the primary and secondary composite endpoints, CV mortality, and all-cause mortality were balanced. Given these characteristics, the hHF finding is manageable through labelling and good medical practice. Appropriate communication of this observation in the Prescribing Information will allow health care providers and patients to take steps during routine diabetes clinical care to potentially prevent hHF for those at high risk of HF. Patients with HF and diabetes need treatment options to help control their diabetes. However, treatment options for these patients are limited, because some agents are contraindicated in HF or associated with heightened risks, such as hypoglycemia and weight increase (Inzucchi et al 2012). Furthermore, there is limited randomized controlled study information available for most antihyperglycemic classes and agents in the setting of HF, limiting evidence-based treatment decisions for these patients. Therefore, considering the overall balanced primary and secondary endpoints in high-risk HF patients, the low risk of hypoglycemia, weight neutrality, and overall balanced AEs and SAEs, saxagliptin remains an important treatment option for these patients.

Importantly, AstraZeneca continues to characterize the overall safety profile of saxagliptin through ongoing pharmacovigilance activities and its clinical program. With regard to the finding of hospitalizations for HF from SAVOR, the Sponsor is undertaking a mechanistic study to evaluate saxagliptin treatment in patients with HF and will evaluate HF hospitalizations in pharmacoepidemiology studies.

In conclusion, the SAVOR study has contributed significantly to AstraZeneca’s understanding of the safety of saxagliptin. AstraZeneca’s clinical program has established the efficacy of saxagliptin in reducing HbA1c and this program along with the postmarketing safety data have shown that saxagliptin is well tolerated. The totality of the clinical data with saxagliptin shows that, when used according to the label, saxagliptin has a favorable benefit:risk profile and remains an important treatment option for patients with T2DM.

10. REFERENCES

Web links are provided for references with open access.

ADA 2015
American Diabetes Association. Standards of medical care in diabetes—2015. Diabetes Care 2015;38 Suppl 1: S33-40. Available at:
http://care.diabetesjournals.org/content/38/Supplement_1/S33.full.pdf+htmlBraunwald 2013

Braunwald 2013
Braunwald E. Heart Failure. JACC: Heart Failure 2013;1:1-20.

Cobble and Frederich 2012
Cobble ME, Frederich R. Saxagliptin for the treatment of type 2 diabetes mellitus: assessing cardiovascular data. Cardiovasc Diabetol 2012;11:1-8. Available at:
http://www.cardiab.com/content/11/1/6

Cryer 2014
Cryer PE. Glycemic goals in diabetes: Trade-off between glycemic control and iatrogenic hypoglycemia. Diabetes 2014;63:2188-95. Available at:
http://diabetes.diabetesjournals.org/content/63/7/2188.long

DCCT 1993
The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–86. Available at:
http://www.nejm.org/doi/pdf/10.1056/NEJM199309303291401

EMA Revised Guidance on Diabetes Mellitus 2012
European Medicines Agency. Guideline on clinical investigational medicinal products in the treatment or prevention of diabetes mellitus CPMP/EWP/1080/00 Rev 1. 14 May 2012. Committee for Medicinal Products for Human Use (CHMP). Available at:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf

FDA Draft Guidance on Diabetes Mellitus 2008
Food and Drug Administration. Draft Guidance for Industry. Diabetes Mellitus: Developing drugs and therapeutic biologics for treatment and prevention. Draft Guidance. February 2008. US Department of Health and Human Services, Center for Drug Evaluation and Research. Available at: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071624.pdf

FDA Final Guidance on Diabetes Mellitus 2008
Food and Drug Administration. Final Guidance for Industry Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. December

2008. US Department of Health and Human Services, Center for Drug Evaluation and Research. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

Felker et al 2007
Felker GM, Allen LA, Pocock SJ et al. Red cell distribution width as a novel prognostic marker in heart failure. J Am Coll Cardiol 2007;50:40-47. Available at: http://ac.els-cdn.com/S0735109707012703/1-s2.0-S0735109707012703-main.pdf?_tid=1eb4982c-c0ee-11e4-b3a5-00000aacb361&acdnat=1425309147_6858931773854dccdd9d2201ddea1c8e

Frederich et al 2010
Frederich R, Alexander JH, Fiedorek FT, Donovan M, Berglind N, Harris S, et al. A systematic assessment of cardiovascular outcomes in the saxagliptin drug development program for type 2 diabetes. Postgrad Med 2010;122:16-27.

Hicks et al 2010
Hicks KA, Hung HMJ, Mahaffey KW, Mehran R, Nissen SE, Stockbridge NL, et al, on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative. Standardized definitions for end point events in cardiovascular trials. November 2010. Available at: http://www.clinpage.com/images/uploads/endpoint-defs_11-16-2010.pdf

Hirshberg et al 2014
Hirshberg B1, Parker A, Edelberg H, Donovan M, Iqbal N. Safety of saxagliptin: events of special interest in 9156 patients with type 2 diabetes mellitus. Diabetes Metab Res Rev 2014;30:556-69. doi: 10.1002/dmrr.2502.

Inzucchi et al 2012
Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–79. Available at: http://care.diabetesjournals.org/content/35/6/1364.long

Iqbal et al 2014
Iqbal N, Parker A, Frederich R, Donovan M, Hirshberg B. Assessment of the cardiovascular safety of saxagliptin in patients with type 2 diabetes mellitus: pooled analysis of 20 clinical trials. Cardiovasc Diabetol 2014;13:33. Available at: http://www.cardiab.com/content/pdf/1475-2840-13-33.pdf

Lachin 2000
Lachin JM. Statistical considerations in the intent-to-treat principle. Control Clin Trials 2000;21:167-89.

Levy et al 2006
Levy AS, Coresh J, Greene T, Stevens, LA, Zhang YL, Hendriksen S, et al. Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145(4):247-54.

Malandrino et al 2012
Malandrino N, Wu WC, Taveira TH, Whitlatch HB, Smith RJ. Association between red blood cell distribution width and macrovascular and microvascular complications in diabetes. Diabetologia 2012;55:226-35. Available at:
http://link.springer.com/article/10.1007%2Fs00125-011-2331-1

O'Connor et al 2008
O'Connor, CM, Abraham WT, Nancy M. Albert, NM, Clare R, Gattis-Stough W, Gheorghiade M, et al. Predictors of mortality after discharge in patients hospitalized with heart failure: An analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). Am Heart J 2008;156:662-73.

O'Meara et al 2006
O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Lang CC, Roger SD, et al. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. Circulation 2006 Feb 21;113(7):986-94. Available at:
http://circ.ahajournals.org/content/113/7/986.full.pdf+html

ONGLYZA® USPI
ONGLYZA® (saxagliptin). United States Prescribing Information. Astrazeneca Pharmaceuticals, Inc.; updated June 2014. Available at:
http://www.azpicentral.com/onglyza/pi_onglyza.pdf#page=1

Rydén et al 2013
Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. European Heart Journal 2013;34: 3035–87. Available at:
http://eurheartj.oxfordjournals.org/content/ehj/34/39/3035.full.pdf

Skyler et al 2009
Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EAM, et al. Intensive glycaemic control and the prevention of cardiovascular events: Implications of the ACCORD, ADVANCE, and VA diabetes trials: A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care 2009;32:187-92. Available at:
http://care.diabetesjournals.org/content/32/1/187.full.pdf+html

UKPDS Group 1998
The UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53.

Usher and Drucker 2012
Usher JR, Drucker DJ. Cardiovascular biology of the incretin system. Endocrine Reviews. 2012;33:187-215. Available at: http://press.endocrine.org/doi/pdf/10.1210/er.2011-1052

Uthamalingam et al 2011
Uthamalingam S, Patvardhan EA, Subramanian S, Ahmed W, Martin W, Daley M, et al. Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure. Am J Cardiol 2011;107:433-8.

Zannad et al 2013
Zannad F, Garcia AA, Anker SD, Armstrong PW, Calvo G, Cleland JGF, et al. Clinical outcome endpoints in heart failure trials: a European Society of Cardiology Heart Failure Association consensus document. Eur J Heart Failure 2013;15:1082:94. Available at: http://onlinelibrary.wiley.com/doi/10.1093/eurjhf/hft095/epdf

Appendix to Advisory Committee Briefing Document - Publications

Drug Substance Saxagliptin

SAVOR

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus

sNDAs for Onglyza (22-350/S-014) and Kombiglyze (200-678/S-013)

Briefing Document for Endocrinologic and Metabolic Drugs Advisory Committee Meeting

Appendix A Properties of available glucose-lowering agents

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

TABLE OF CONTENTS PAGE

LIST OF TABLES

Table 1 Properties of glucose-lowering agents in the US and Europe that may guide individualized treatment in patients with T2DM 3

Table 1 Properties of glucose-lowering agents in the US and Europe that may guide individualized treatment in patients with T2DM

Class	Advantages	Disadvantages
Biguanides	Extensive experience No hypoglycemia ↓ CVD events (UKPDS)	Gastrointestinal side effects (diarrhea, abdominal cramping) Lactic acidosis risk (rare) Vitamin B12 deficiency Multiple contraindications: CKD, acidosis, hypoxia, dehydration, etc.
Sulfonylureas	Extensive experience ↓ Microvascular risk (UKPDS)	Hypoglycemia ↑ Weight ? Blunts myocardial ischemic preconditioning Low durability
TZDs	No hypoglycemia Durability ↑ HDL-C ↓ Triglycerides (pioglitazone) ? ↓ CVD events (PROactive, pioglitazone)	↑ Weight Edema/heart failure Bone fractures ↑ LDL-C (rosiglitazone) ? ↑ MI (meta-analyses, rosiglitazone)
DPP-4 inhibitors	No hypoglycemia Well tolerated	Angioedema/urticaria and other immune-mediated dermatological effects ? Acute pancreatitis ? ↑ Heart failure hospitalizations
SGLT2 inhibitors	No hypoglycemia ↓ Weight ↓ Blood pressure Effective at all stages of T2DM	Genitourinary infections Polyuria Volume depletion/hypotension dizziness ↑ LDL-C ↑ Creatinine (transient)

Class	Advantages	Disadvantages
GLP-1 receptor agonists	No hypoglycemia ↓ Weight ↓ Postprandial glucose excursions ↓ Some CV risk factors	Gastrointestinal side effects (nausea/vomiting/diarrhea) ↑ Heart rate ? Acute pancreatitis C-cell hyperplasia/medullary thyroid tumors in animals Injectable Training requirements
Insulins	Nearly universal response Theoretically unlimited efficacy ↓ Microvascular risk (UKPDS)	Hypoglycemia Weight gain ? Mitogenic effects Injectable Patient reluctance Training requirements

CKD Chronic kidney disease; CV Cardiovascular; CVD Cardiovascular disease; DPP-4 Dipeptidyl peptidase-4; GLP-1 Glucagon-like peptide-1; HDL-C High-density lipoprotein-cholesterol; LDL-C Low-density lipoprotein-cholesterol; MI Myocardial infarction; T2DM Type 2 diabetes mellitus; TZD Thiazolidinedione; UKPDS UK Prospective Diabetes Study.

Adapted from ADA Guidelines, Diabetes Care Vol 38 January 2015:142-3.

Appendix to Advisory Committee Briefing Document - Publications

Drug Substance Saxagliptin

SAVOR

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus

sNDAs for Onglyza (22-350/S-014) and Kombiglyze (200-678/S-013)

Briefing Document for Endocrinologic and Metabolic Drugs Advisory Committee Meeting

Appendix B SAVOR TIMI 53 Publications

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

TABLE OF CONTENTS PAGE

TABLE OF CONTENTS 2
SAVOR TIMI-53 PUBLICATIONS 3

SAVOR TIMI-53 PUBLICATIONS (LINKS)

Scirica et al 2011

Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. The design and rationale of the Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus-Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 Study. Am Heart J 2011;162:818-25. doi: 10.1016/j.ahj.2011.08.006

Available at: http://www.ahjonline.com/article/S0002-8703%2811%2900622-3/pdf

Scirica et al 2013

Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317-26. doi: 10.1056/NEJMoa1307684

Available at: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1307684

Supplementary appendix available at:
http://www.nejm.org/doi/suppl/10.1056/NEJMoa1307684/suppl_file/nejmoa1307684_appendix.pdf

Scirica et al 2014

Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation 2014;130(18):1579-88. doi: 10.1161/CIRCULATIONAHA.114.010389

Available at: http://circ.ahajournals.org/content/130/18/1579.full.pdf+html